THE
RICE INSTITUTE PAMPHLET

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A university of liberal and technical learning
ounded by William Marsh Rice in the City
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LECTURES ON SUBJECTS IN PHYSICS, CHEMISTRY AND BIOLOGY

I

THE ULTIMATE PARTICLES: ELECTRONS, PROTONS, PHOTONS, AND NEUTRONS

THE idea that matter consists of minute indivisible particles or atoms is as old as philosophy, but it did not lead to anything of importance until Dalton developed his chemical atomic theory early in the nineteenth century. According to Dalton's theory each chemical element was supposed to consist of exactly equal atoms which were thought of as minute hard indivisible particles.

The relative weights of the atoms of different elements were calculated from the percentage composition of compounds. For example, sulphur dioxide contains fifty per cent by weight of sulphur and fifty per cent of oxygen, so that since it is found to contain two atoms of oxygen to one of sulphur it follows that the weight of an atom of sulphur is just twice that of an atom of oxygen. In the same way water contains 11.18 per cent of hydrogen and two hydrogen atoms to one of oxygen, so that an oxygen atom must be 88.85/5.59 or 15.88 times as heavy as an atom of hydrogen. Taking the atomic weight of oxygen to be 16, the atomic weights of sulphur and hydrogen are therefore 32.00 and 1.0077.

In this way chemists determined the relative weights of the atoms of all the known elements. It was found that some of the atomic weights, taking that of oxygen to be 16, were whole numbers, for example, carbon 12.00, nitrogen 14.00, sodium 23.00. Also many atomic weights were not whole numbers, for example, chlorine 35.46 and silver 107.88. Until nearly the end of the nineteenth century Dalton's chemical atoms were supposed to be the ultimate particles of matter. All the atoms of any one element were thought of as minute exactly equal hard indivisible particles. It was supposed that these atoms excited fields of force in the space around them so that they could attract or repel each other when very near together. The differences between the properties of the different elements were attributed to differences between the fields of force excited by their atoms.

In solid bodies it was supposed that the atoms were rather tightly packed so that nearly all the space occupied by a solid was filled up with hard indivisible particles.

Electricity was thought of as an immaterial fluid with which atoms could be charged. An electric current in a copper wire was thought of as a flow of this fluid from one atom to another in the copper. The electric fluid was not regarded as an essential constituent of the atoms.

These nineteenth century ideas about matter and electricity have turned out to be erroneous. We do not now regard atoms as indivisible particles and it is found that the atoms of any element are not all equal. The atomic weights as found by chemists have turned out to be merely average values not equal to the true relative weights of the atoms. Electricity is no longer thought of as an immaterial fluid but is found to consist of material atoms out of which the atoms of the chemical elements are constructed. Matter in fact is just electricity and nothing else.

In this lecture I am going to try to outline briefly the experimental results and the arguments based on them which have led to such revolutionary conclusions.

The collapse of the old ideas began about 1897 when J. J. Thomson at the Cavendish Laboratory in England showed that particles more than a thousand times lighter than hydrogen atoms could be obtained from any kind of matter. These particles were called electrons. Electrons escape from any substance at a high enough temperature. They come off hot bodies just like vapor from a hot liquid. Electrons are just particles of negative electricity, so a very hot body in a good vacuum loses negative but not positive electricity. This evaporation of electrons from a hot body in a vacuum may be shown experimentally with an apparatus consisting of a large glass bulb containing a tungsten wire like the filament of an electric light bulb. The wire is inside a metal cylinder in the large bulb and when the wire is made white hot by passing a current through it the electrons escape from the wire so that a current of negative electricity can be passed through the vacuum from the hot wire to the surrounding cylinder. But no current will flow in the opposite direction because no positive electricity escapes from the hot wire. Electrons are attracted by positive electricity and repelled by negative, as we should expect. They are deflected sideways in a magnetic field just as an electric current in a wire is deflected.

J. J. Thomson studied the motion of electrons in electric and magnetic fields and showed that they behave like particles of negative electricity. He found that the amount of electricity carried by a unit weight of electrons was very large, about two thousand times greater than the amount carried by unit weight of charged hydrogen atoms.

Now Faraday had shown that electrically charged atoms carry charges which are always small multiples of the charge carried by a hydrogen atom. For example, he found that an oxygen atom carries just twice as much electricity as a hydrogen atom and an iron atom just three times as much. These results of Faraday suggested that electricity is made up of equal atoms and that a charged hydrogen atom carries one such atomic unit of electricity, an oxygen atom two, and an iron atom three.

J. J. Thomson adopted this idea and supposed that his electrons were the atoms of negative electricity. Since he found the charge per unit weight of the electrons to be two thousand times greater than for charged hydrogen, it followed, if the electrons and the hydrogen atoms carried equal charges, that the weight of an electron was two thousand times smaller than that of a hydrogen atom. This assumption has since been proved to be correct. Thus it appears that all substances contain electrons which are very much lighter particles than the chemical atoms. Also it is found that all atoms contain electrons. Thus for example when X-rays are passed through a gas they knock electrons out of the gas atoms.

J. J. Thomson's results, which have been confirmed and extended by many other physicists, showed clearly that atoms are not hard indivisible particles but are complicated structures containing electrons.

Electrons are just particles of negative electricity, so that it is clear that an electrically neutral atom must contain positive electricity as well as electrons. The total amount of positive charge in an electrically neutral atom must be exactly equal to the total negative charge. The negative charge in the atom is always an exact multiple of that of one electron so that the positive electricity in the atom must also be made up of atomic units equal to the electronic charge. We should therefore expect to find particles of positive electricity in atoms equal to the electrons. It is found that atoms do contain particles of positive electricity having charges equal though of opposite sign to the negative charges of electrons, but the positive particles are about two thousand times heavier than the negative particles or electrons. The positive particles are called protons. It is not possible to make protons escape from hot bodies like electrons, and the arguments for the existence of protons in atoms are less direct, though not less convincing, than those for the existence of electrons.

When an electric current is passed through a gas at a low pressure it is found that the current is carried by electrons moving in one direction and positively charged atoms moving in the opposite direction. The stream of positively charged atoms can be allowed to pass through a hole in the negative electrode and so may be separated from the stream of electrons. Such a stream of positively charged atoms is called a beam of positive rays and the properties of these positive rays have been very carefully investigated mainly by J. J. Thomson and Aston in the Cavendish Laboratory.

Aston devised a method of studying these rays in which they are deflected by electric and magnetic fields and then allowed to fall on a photographic plate. The fields are so designed that the position at which the rays strike the plate is determined by the weight per unit charge of the rays. Thus the positive rays are separated into groups, all those in any one group having the same weight per unit charge. Each group makes a line on the photographic plate and the position of the line is determined by the weight per unit charge of the rays in the group.

The charge on a positively charged atom is always a multiple of the positive charge equal to the negative charge of an electron. For if we start with an electrically neutral atom and then remove one electron from it, we get an atom with a positive charge equal to the negative charge on one electron. If we then imagine that the atom loses another electron, its positive charge is doubled, and so on. The weight per unit charge for the atom is equal to its atomic weight divided by the number of electrons which it has lost. For example, an oxygen atom of atomic weight 16, which has lost two electrons and so has two units of positive charge, has weight per unit charge equal to 8. In the same way a mercury atom of atomic weight 200 which has lost four electrons has weight per unit charge 200/4 or 50.

With his positive ray apparatus Aston was able to measure the weight per unit charge for the rays obtained from any element with great accuracy and so was able to determine the relative weights of the atoms in the rays.

Now the relative weights of the atoms have been determined by the chemists, and so we should have expected Aston's results to agree with the chemical atomic weights. However this has not proved to be the case. In the first place, Aston finds that the atomic weights, taking that of oxygen to be 16, are all very nearly whole numbers. For example, he finds the atomic weight of chlorine to be 35.00, whereas according to the chemists it is 35.45. In the same way he finds 200 for the atomic weight of quicksilver, while the chemical atomic weight is 200.6. The chemical determinations of atomic weights really only give the average atomic weight of an enormous number of atoms which are assumed to all have equal weights. Aston's method gives the actual weight of the atoms which fall on his photographic plate at a given place because any atoms with a different weight would go to a different place.

It is clear therefore that Aston's results are correct, so that it appears that the true atomic weights of the elements are equal to whole numbers or integers when that of oxygen is taken to be 16. The only plausible explanation of this result, which has been suggested, is that the atoms are built up out of units of atomic weight one. Also since, as we have seen, atoms must contain units of positive electricity equal to the negative charge on electrons, it is natural to suppose that the units of atomic weight one have also equal positive charges equal but of opposite sign to the electronic charge. We are thus led to regard the atoms of all the different chemical elements as built up out of only two different sorts of particles, namely, electrons and positively charged particles of atomic weight one, which are called protons. The atomic weight of hydrogen is nearly one, so an electrically neutral hydrogen atom should consist of one proton and one electron. It should be observed here that since any neutral atom contains as many electrons as protons, the atomic weight unity is really the sum of the atomic weights of an electron and a proton, but that of the electron is so small, only about 0.0005, that it is negligible.

The atomic weight of hydrogen however is an exception to Aston's rule that the atomic weights are whole numbers. It is 1.0077 according to Aston and also as determined by the chemists. The atomic weight of helium is 4.000 so a neutral helium atom should consist of four protons and four electrons and so if a hydrogen atom is one proton and one electron, either the atomic weight of hydrogen should be 1.000 or else that of helium should be 4×1.0077 or 4.0308 which is certainly not the case. It appears that if helium could be prepared from hydrogen there would be a loss of weight so that 4.0308 pounds of hydrogen would only give 4.000 pounds of helium.

It is believed that this anomaly can be explained by supposing that in order to convert hydrogen into helium it would be necessary to remove a large amount of energy from the hydrogen and that the loss of weight is just the weight of the energy which would have to be removed.

Aston also obtained another result of fundamental importance. He found that atoms of several different weights but all of the same chemical element exist. Thus, for example, he found chlorine to be a mixture of atoms having atomic weights 35 and 37. These two sorts of atoms are present in ordinary chlorine in such proportions that the average atomic weight is 35.45 which is the value found by chemical methods.

We are thus led to conclude that the atoms of all the chemical elements are not indivisible particles but are formed out of just two sorts of ultimate particles, namely, electrons and protons. Electrons and protons, moreover, are just electricity and nothing else. The ninety-two different chemical elements are therefore not really elements at all, in the old sense of the word, but are all compounds of electrons and protons. They are nevertheless still called elements because they cannot be split up into electrons and protons by ordinary chemical processes.

Besides electrons and protons there is another sort of ultimate particle the existence of which has been demonstrated in recent years. These particles are called photons and they are quite different from electrons and protons. Photons are found in light, in fact we may say that light is just a stream of photons. Now light is emitted by very hot bodies, for example, the ordinary electric light bulb is just a glass bulb containing a loop of fine wire which is made very hot by passing a current of electricity through it. Such a hot wire as we have seen emits electrons but it also emits light which consists of photons. The emission of electrons is supposed to show that the wire contains electrons, so we might suppose that the wire must also contain photons, since it emits them when hot. However a photon is a much less material sort of particle than an electron, and it is customary to believe that photons are generated in the wire out of nothing but energy before they are emitted.

Light is believed to consist of photons because the effects produced by light are such as might be expected to be produced by a stream of particles. Consider, for example, the action of light on a photographic plate. Such a plate is coated with a thin layer of gelatine containing minute grains of silver bromide. When the plate is developed, after being exposed to weak light for a short time, it is found that a few of the grains have been changed by the light but that the majority of them are quite unaffected. This can be explained by supposing the light to consist of particles or photons for then only those grains of silver bromide should be affected which happen to be hit by a photon. If light consisted of waves as was formerly supposed we should expect all the grains to be equally affected, which is not the case.

The particle nature of light can be most clearly demonstrated by using X-rays which are of the same nature as light but have photons of much greater energy.

X-rays are obtained by allowing a stream of electrons of high energy to fall on a metal plate. The electrons collide with the metal atoms in the plate and excite them so that they emit X-rays.

When X-rays are passed through a gas like air they cause a few of the gas atoms to emit electrons. This effect can be demonstrated very clearly by the beautiful method developed by C. T. R. Wilson of the Cavendish Laboratory.

The X-rays are passed through air supersaturated with water vapor and the electrons emitted by the air atoms then produce visible tracks consisting of minute drops of water which can be photographed in a bright light. In this way a permanent record of the electron tracks is obtained. The length of these electron tracks depends on the energy of the electrons and it is found that the energy of these electrons is just equal to that of the energy of the electrons used to produce the X-rays.

Thus an electron having kinetic energy hits a metal atom which emits an X-ray. The X-ray travels a long distance, perhaps 100 feet, and then hits a gas atom and causes the gas atom to emit an electron with the same kinetic energy as that of the first electron which hit the metal atom 100 feet away. It is clear that the energy of the first electron must have travelled from the metal atom to the gas atom. This can only be explained by supposing that the X-ray is a particle which carries the energy from the metal atom to the gas atom. The energy could not be transmitted in this way by waves because waves diverge in all directions and so could only carry a minute fraction of the energy of the first electron from the metal atom to the gas atom.

It appears therefore that light and X-rays consist of particles which are called photons. Photons always move along with the velocity of light, 186,000 miles a second. The color of light depends on the energy of the photons. The photons in violet light have about twice as much energy as those in red light and X-ray photons have about ten thousand times as much energy as those of violet light.

Photons do not have an electric charge like electrons and protons; they have nothing but kinetic energy, so if a photon loses its kinetic energy it disappears. A photon cannot be stopped without being destroyed because to stop it is to take away its kinetic energy. Electrons and protons can be stopped and still exist because they are particles of electricity. When they are moving they have kinetic energy like photons but they do not disappear when stopped because of their charges.

The rays from an X-ray tube diverge in all directions, so that the greater the distance from the tube the weaker the rays. It is found that the very weak rays at a great distance from an X-ray tube knock electrons out of atoms with exactly the same energy as the intense rays close to the tube. Near the tube more electrons are knocked out than farther away, but the energy of each electron is the same at any distance. This result cannot be explained on the wave theory of X-rays, but it is easily explained on the particle theory. The rays emitted by radioactive elements like radium are of three kinds: photons, electrons, and alpha-rays. No protons are emitted which is perhaps rather surprising. The alpha-rays are found to be helium atoms which have lost two electrons. A neutral helium atom consists of four protons and four electrons, so an alpha-ray is four protons and two electrons which are closely combined together into a very small particle. Thus an alpha-ray is positively charged; it has twice the charge and four times the weight of a proton.

Alpha-rays make visible tracks in air supersaturated with moisture just as electrons do, but the alpha-ray tracks are very different from electron tracks. The alpha-ray tracks are straight and much thicker than the electron tracks, which are not straight but irregularly curved. The alpha-rays are nearly 4000 times as heavy as electrons and so are not so easily deflected by collisions. A particle like an electron or an alpha-ray moving rapidly through a gas like air collides with many thousands of atoms while it moves one inch. The electrons are deflected by these collisions but the alpha-rays are not. Now when a rapidly moving body collides with another body we should expect it to be deflected unless it is very much heavier than the body with which it collides. For example, a motor car weighing 4000 pounds is not appreciably deflected by a collision with a stone weighing one pound, but is seriously affected by a collision with another car. We are forced therefore to conclude that electrons and alpha-rays moving rapidly through a gas only collide with the electrons in the gas atoms. An electron is deflected by a collision with another electron but an alpha-ray which is 4000 times as heavy as an electron is not appreciably deflected by a collision with one. But, as we have seen, atoms contain as many protons as electrons, so we might have expected as many collisions with protons as with electrons. An alpha-ray is only four times as heavy as a proton and so should be appreciably deflected by a collision with one. It appears therefore that, although atoms contain as many protons as electrons, yet the protons must only occupy a very small fraction of the space in an atom, so that an alpha-ray moving through the atoms in a gas hardly ever hits a proton although it hits electrons in every atom it passes through.

When a large number of alpha-ray tracks is examined it is found that a few are sharply bent through appreciable angles. These rare deflections are supposed to be caused by collisions with the protons. A study of such deflections of alpha-rays led Lord Rutherford to propose his nucleus theory of the atom according to which the protons and about half the electrons in an atom are closely packed into a very small nucleus, while the rest of the electrons are outside the nucleus moving about round it. For example, an oxygen atom has a nucleus containing 16 protons and 8 electrons, and there are 8 electrons outside the nucleus. The chemical properties of the atoms are determined by the number of electrons outside the nucleus. Thus, for example, chlorine atoms all have 17 outside electrons, although some chlorine atoms contain 35 protons and some 37. All the atoms of any one element are alike as regards their outside electrons, although they may not all have the same number of protons in their nuclei.

Up to early in the year 1932 matter and radiation were supposed to be made of electrons, protons, and photons and nothing else. In that year, however, the existence of a fourth type of ultimate particle was discovered. These new particles are called neutrons.

Bothe and Becker, in Germany, in 1930 found that solid elements of small atomic weight, like lithium, boron, and beryllium, when exposed to alpha-rays emit a very penetrating radiation which they supposed probably consisted of photons. This radiation was studied by I. Curie and Joliot in France, and by Chadwick in England.

Chadwick showed that this penetrating radiation did not have the properties of photons, but that its properties were such as could be explained by assuming it to consist of particles of atomic weight one not having any electric charge. He proposed to call these particles neutrons.

When photons are passed through air supersaturated with moisture they do not produce any visible track themselves but they knock electrons out of the air atoms and these electrons produce thin irregularly curved tracks.

Protons and alpha-rays produce straight thick tracks very rarely bent appreciably by collisions with atomic nuclei. Neutrons, or the penetrating radiations from beryllium bombarded by alpha-rays, behave like photons in not producing any tracks themselves but do not knock electrons out of the air atoms and so produce no electron tracks. They do, however, produce a very few short thick tracks such as might be due to air atoms moving with a high velocity.

Now protons and alpha-rays, when they hit the nucleus of an atom and are so appreciably deflected, impart enough energy to the atom to cause it to produce a short thick track. In such cases the short thick track appears as a branch track branching from the alpha-ray track at the point where it is deflected.

Thus neutrons resemble photons in not producing tracks themselves and resemble protons and alpha-rays in colliding with atomic nuclei and causing these nuclei to make short thick tracks.

Also it is found that neutrons when passed through paraffin wax, which contains hydrogen, knock protons but no electrons out of the wax, while photons do not knock protons out of such wax but only electrons.

It is clear therefore that neutrons are quite different from photons, electrons, protons, or alpha-rays.

Charged particles like electrons, protons, and alpha-rays produce visible tracks while photons which are not charged do not. Since neutrons produce no visible tracks themselves we conclude that they are not electrically charged and so resemble photons in this respect.

Neutrons, protons, and alpha-rays collide with the nuclei of atoms and cause the atoms to produce short thick tracks. We conclude that neutrons are relatively heavy particles like protons and alpha-rays. Feather, working in the Cavendish Laboratory with Chadwick, has shown that neutrons passing through nitrogen sometimes produce V-shaped tracks which are believed to be due to the neutron knocking an alpha-ray out of a nitrogen atom. The alpha-ray recoils in one direction and the rest of the nitrogen atom in another, so making the V.

The atomic weight of nitrogen is 14 and that of an alpha-ray is 4, so that if an alpha-ray is knocked out of a nitrogen atom a particle of atomic weight 10 remains. But there is no known substance of atomic weight 10, so it seems probable that the atomic weight of the neutron is one and that the neutron is captured by the nitrogen atom so giving a particle of atomic weight 11, which is boron. When boron is bombarded by alpha-rays, neutrons are emitted. A boron atom of weight 11 and an alpha-ray of weight 4 give a nitrogen atom of weight 14 and a neutron of weight one. The lengths and directions of the short thick tracks observed when neutrons are passed through air supersaturated with moisture are found to be such as might be expected to be produced by a collision of a particle of atomic weight one with an air atom.

There are therefore good reasons for believing neutrons to be uncharged particles of atomic weight one.

Very recent observations by Anderson at the California Institute of Technology suggest the existence of particles like electrons but positively instead of negatively charged. These observations have already been confirmed in Cambridge.

We have then at present as ultimate particles: photons, negative electrons, positive electrons, protons, and neutrons. Perhaps it may turn out that a proton is a combination of a neutron and a positive electron, or that a neutron is a combination of a proton and a negative electron. The discovery of neutrons and positive electrons makes the constitution of atoms uncertain. With only electrons and protons it was clear that atoms contained equal numbers of these two sorts of particles. But with neutrons and positive electrons as well we cannot tell how many electrons there are in an atom. For example, the nucleus of a chlorine atom of atomic weight 35 with 17 outside negative electrons might contain

35 neutrons and 17 positive electrons, or say 18 neutrons and 17 protons, or any other combination which would give a nucleus of weight 35 and positive charge 17.

The discovery of positive electrons is of fundamental importance and raises all sorts of interesting questions. For example, why is it so easy to get negative electrons out of matter but so difficult to get positive electrons out that they have escaped detection until now? Do metals like copper contain free positive electrons as well as free negative electrons? If both sorts of free electrons are present then a current in a copper wire is a stream of positive electrons going one way and negative electrons going the other way and not merely negative electrons going one way as has been supposed for many years.

Much experimental and theoretical investigation will be required before such questions can be answered.

H. A. Wilson.

II

COSMIC RAYS

INTRODUCTION

THE study of the penetrating radiation now known as cosmic rays has for many years excited a great deal of interest among physicists. This interest is at present on the increase, as indicated by the fact that though one hundred and six papers bearing on this subject were written between about 1907 and 1924, in the next eight years no less than three hundred and seven were published. It is not without wonder that some of the results of these works have reached the ear of the layman and that he should begin to be curious as to what all the fuss over cosmic rays is about. I shall attempt in the following lines to cast a little light on this question.

By way of an introductory definition it may be said that the cosmic radiation is a new type of radiation which is arriving at the earth's surface from somewhere outside of its atmosphere. It is present, as far as we know, at all points on the surface of the earth and has the same intensity, or strength, by night as by day.

This radiation is similar in its properties to the well known X-rays and to the radiation from radioactive substances. One important property of these radiations is their ability to ionize materials through which they pass. Ionization means simply the splitting of a part of the atoms or molecules of a substance into positively and negatively charged particles. This ionizing ability is made use of in studying the radiation and is responsible for its discovery. The ionization is detected or measured by instruments identical in principle with the familiar gold-leaf electroscope. A diagram of a modern cosmic-ray electroscope is presented in

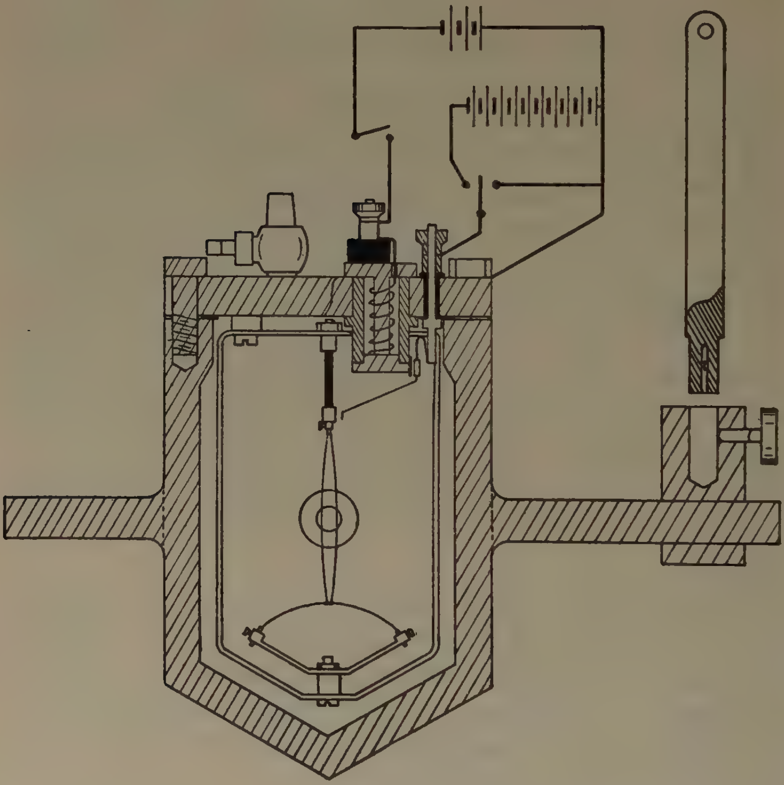

FIGURE 1.

Fig. 1. In this instrument the gold leaves have been replaced by a pair of very fine quartz fibers, coated with platinum to render them conducting. They are attached at their upper ends to an insulating quartz rod, which is in turn supported from the cover of the case. At their lower ends they are attached to a fine insulating quartz bow for

the purpose of maintaining their position in the vertical plane. By means of a movable wire, which can be brought momentarily into contact with the upper ends of the fibers, an electric charge can be placed on them. They will then spread apart under the influence of their mutual electrostatic repulsion, the amount of spreading being a measure of the amount of electricity (quantity of charge) they possess. The fibers are enclosed in an airtight case containing, in this particular instrument, argon gas. Now if an ionizing radiation is falling on the instrument and is generating ions in the gas, the ions of the proper sign will be attracted to the charged fibers and will gradually neutralize their charge. Accordingly, the fibers will be observed gradually to come together, and the rate at which they do so will be a measure of the intensity of the radiation. The motion of the fibers is observed by means of a low-power microscope carrying a measuring scale in its eye piece. It is mounted outside the case, vision into the interior of the instrument being through a small glass window in its side. By means of instruments similar to this the cosmic radiation was discovered and numerous studies have been made of its intensity under various conditions, such as, for example, the way in which the intensity increases with increasing altitude above sea-level.

DISCOVERY AND EARLY EXPERIMENTS

The first step toward the discovery of the cosmic radiation came as early as the year 1900 when Elster and Geitel observed that an electroscope always showed a slow discharge though in the absence of an artificial source of ionizing radiation. It was later shown that this discharge is principally due to the radiation from traces of radioactive materials which are always present in the soil, in building materials, or even in the materials of the electroscope itself. This observation, however, led Gockel in 1910 to take an electroscope up in a balloon for the purpose of making observations on the rate of discharge in what he believed to be a practically radiation-free region. It was known that the radiation from the ground radioactivity should be reduced to a vanishingly small intensity at an altitude of a few thousand feet on account of its absorption by the intervening air. Gockel was surprised to find that the rate of discharge of his electroscope remained roughly constant, where he expected that it would fall to low values, indicating very little radiation. His unexpected result was not at that time believed to indicate more than some hidden source of experimental error. However, the same experiment was repeated by Hess in the next year and constituted the first definite indication of the presence in the atmosphere of this hitherto unsuspected radiation. Hess found that the rate of discharge of his electroscope actually increased considerably as the altitude increased, after going through a minimum value where the radiation from the ground had all been absorbed by the intervening air. This result indicated the presence of radiation coming down from above and being gradually reduced in intensity in the course of its passage through the atmosphere. Numerous experiments of this nature were subsequently performed, all showing the same sort of effect. An example of the curve giving the way the intensity of the radiation increases with increasing altitude is presented in Fig. 2. It will be noted that the rate of discharge of the electroscope (plotted vertically) rises to a value many times higher than that at near sea level as the altitude is increased to about 30,000 feet, and is still increasing rapidly on the upper part of the curve. New experiments, reported last summer, in which an automatic recording electroscope was sent up by a small unmanned balloon showed that the intensity continues to rise up to an altitude of about 100,000 feet. The intensity at this altitude, where practically the entire atmosphere had been left behind, was found to be over one hundred times the intensity at sea-level.

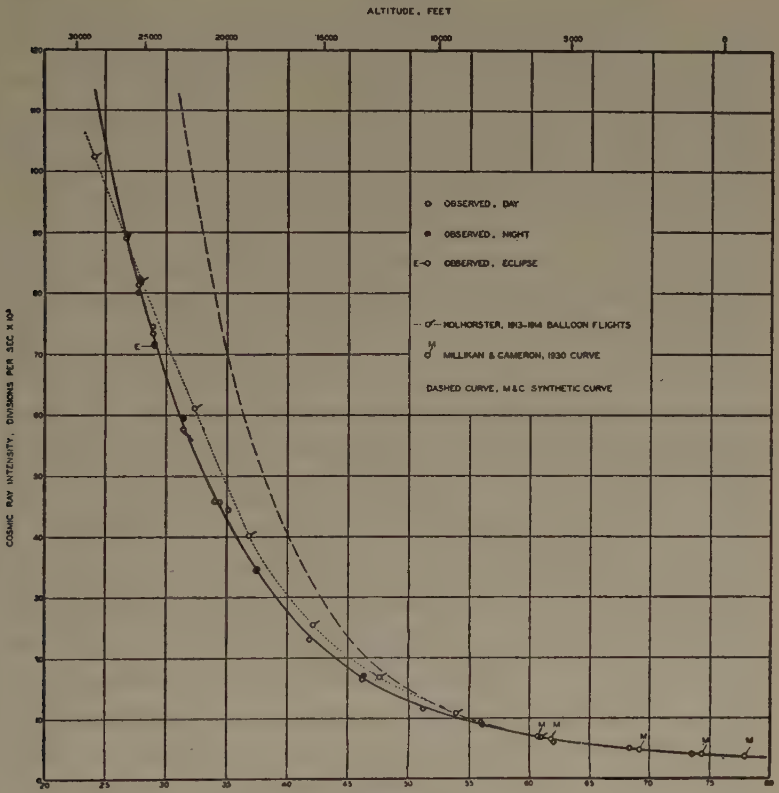

FIGURE 2.

The significance of this result is two-fold. In the first place it seems certain that the radiation is coming down from above. Secondly, from the observed rate of decrease of the intensity it could be concluded that these rays must be enormously more penetrating than any known kinds of ionizing radiations, the most penetrating of which are the gamma-rays from radioactive substances. It is known that the most penetrating, or hardest, gamma-ray would be reduced to about half strength in passing through three hundred feet of air at normal pressure. From inspection of the cosmic-ray curve (Fig. 2) it is seen that it requires a considerably greater amount of air to give the same reduction in intensity, particularly at the lower end of the curve. Accordingly, there is little doubt that one is dealing with a totally different and much more powerful type of radiation than that from any known radioactive substance. From these two observations, namely the increase of intensity with altitude and the great penetrating power, it was only a short step to the conclusion that the radiation must be of extra-terrestrial origin. If it were being produced in the upper atmosphere, then it was necessary either to find there some mechanism by which this powerful radiation is being generated or to assume the presence of some sort of super-radioactive element. Concerning the first possibility, attempts have been made to account for the production of the cosmic rays by invoking the strong electric fields present in thunderstorms. These attempts have met with failure. With regard to the second possible assumption, the presence of new types of radioactive substances giving a more penetrating radiation than those known at the surface of the earth, it seemed extremely unlikely that there could be present in the upper atmosphere elements not also found terrestrially. It is of course definitely known that no natural or artificial substances are sources of radiation with the properties of the cosmic rays. Accordingly, the source of the radiation was placed somewhere outside the earth and its atmosphere. It was placed either in the stars or in the diffuse matter which is observed to fill all space, or at least all the space within reach of the telescopes. The interesting question: the source and the mechanism of production of the radiation, is better deferred until after a discussion of the actual nature of the rays, but it may here be admitted that concerning this question all is mere speculation.

THE NEW EXPERIMENTS

Up to the present point any implication concerning the nature of the cosmic radiation has been avoided, except that it is an ionizing radiation. This was done because there are various possible types of ionizing radiation which the cosmic rays might be, and the attempts to learn just what type they are has been the subject of chief interest in this field during the past few years. There are three principal possible types of radiation: First, there is the so-called gamma-type radiation, where the cosmic rays are assumed to be electro-magnetic waves like gamma-rays, X-rays, ordinary light, etc., but of wave-length shorter than the shortest previously known, namely, gamma-rays. They are assumed to be of still shorter wave-length because it is known from experiments with gamma-rays and X-rays that the penetrating power of this type of radiation becomes greater the smaller the wave-length. The second possibility is that the radiation is composed of rapidly moving electrons. In this case it would be similar to the beta-rays from radioactive substances, but the cosmic-ray electrons would have to be endowed with enormously higher energy than that of the beta-rays to give the observed penetrating power. Finally, it might be supposed that the radiation consisted of some other kind of high-speed particle such as hydrogen or helium nuclei or perhaps even heavier particles.

For many years, in fact until 1928, the cosmic rays were believed to belong to the first type, to be similar to gamma-rays. It was natural to do so, because in the case of the radioactive rays the gamma-rays are much more penetrating than the beta-rays, so that it was thought that the cosmic rays must be a sort of super-gamma-ray. In 1928, however, an experiment was performed by Bothe and Kolhoerster which indicated them to be composed of high-speed particles rather than the previously assumed type. Bothe and Kolhoerster's experiment involved a totally different method from that of the earlier work employing electroscopes. They used a then new device, the Geiger-Müller tube-counter, for detecting and studying the radiation.

To understand this experiment we must consider the process by which radiation such as X-rays, γ-rays or other γ-type radiation is absorbed. In the region of short wavelength the principal manner by which the radiation is weakened, or absorbed, is by a process known as the Compton effect. This effect can be pictured very simply as a collision between a corpuscle of the radiation, a photon, with an electron in the absorbing material. In such a collision momentum and energy are conserved in the same way as in a collision between two perfect billiard balls. In these collisions the photon rebounds from the electron, and in doing so loses more or less of its energy (depending on how nearly head-on the collision), thus causing the absorption of the energy in the photon beam. But what is more important for the present argument is that a portion of the energy of the photon goes into the recoiling electron. This energy gives the electron a certain velocity, and if the collision is favorable and the energy of the photon is high, the recoil electron acquires considerable velocity. Now, on account of the famous $h\nu$ relation that the energy of the photon is proportional to its frequency it is easily computed that photons of the penetrating power of the cosmic rays should be producing very high speed electrons as they pass through absorbing matter. A high speed electron such as a beta-particle from a radioactive substance is capable of penetrating through a certain amount of material. It continually loses speed as it goes until its velocity is finally reduced to zero. In a particular substance, air for instance, the distance it can penetrate depends simply on its initial velocity. It is easily computed that recoil electrons from a photon of the energy of cosmic rays can penetrate considerably more material than β-particles from radioactive sources. It may be calculated that on the average a cosmic recoil electron can pass through six inches of water before it is completely stopped, while the fastest radioactive β-particles are known to be able to penetrate only about half an inch.

Bothe and Kolhoerster devised a method for detecting the presence of these particles in the earth's atmosphere, by the use of the Geiger counter, a relatively simple device which registers high speed electrons. It consists of a tube along the axis of which is stretched a fine wire, the whole being enclosed in an airtight container filled with gas at a pressure of about a tenth of an atmosphere. A source of potential of between one and two thousand volts is connected to the cylinder. The wire is earthed through a high resistance.

If a few ions are formed in the space between the cylinder and the wire, they will acquire considerable velocity under the influence of the relatively strong electric field of this region. Under suitable conditions, which must be satisfied for proper operation, these ions will form new ions when they collide with the molecules of the gas. The new ions thus formed will in turn produce further ions, so that a cumulative process is set up by which an enormous multiplication of ionization results. The entire process takes place in a few hundred thousandths of a second, and is also quickly brought to a stop, probably by formation of a surface charge on the cylinder. Thus a momentary pulse of current is produced whenever a few ions are generated in the interior of the counter, this pulse can be amplified by ordinary vacuum tube amplifiers to sufficient amplitude to be registered on a film, or work some sort of counting device. Hence, if a counter is set up, every time an electron either passes through it or is set off by a γ-ray inside it, it gives a discharge. Now for studying cosmic electrons a single counter is not very satisfactory because it is not possible to distinguish between cosmic electrons and those set off by γ-rays from the surroundings or by radioactive impurities inside the counter. To avoid this difficulty, Bothe and Kolhoerster devised what is known as the coincidence method. They argued, if we put two counters near each other, then if an electron passes through the two we should find impulses occurring simultaneously in the pair. If, further, we put enough absorbing material between them so that no radioactive particles can pass through, we shall be recording only cosmic electrons. Of course a few of the coincidences will occur just by chance, but this fraction is readily found by a separate experiment and allowed for. They set up two counters and found the coincidences. The next thing they were interested in was to find the penetrating power of the electrons, to see if it was in agreement with the value calculated from the frequency of the cosmic rays and the laws of the Compton process. Contrary to expectations, they found that the penetrating power of the electrons was the same as that of the cosmic rays themselves. They expected to find that the electrons would be completely prevented from passing by a screen of six inches of water, or an equivalent amount of other materials. For example, if lead were used, since its density is about eleven times that of water, a screen of this material of one-half inch thickness should suffice. Actually they found that the maximum amount of material which they could put between these counters, about one and one-half inches of gold, whose density is of course even greater than that of lead, only stopped about twenty-five per cent of the electrons. Now from the measurements with the electroscopes it was known that this amount of absorbing material would reduce the cosmic rays themselves by about the same fraction. This result appeared to mean that the electrons were the cosmic rays themselves, and that the ionization found in the electroscope was due to them. Of course these high speed electrons as they go through matter are known to produce ionization, so that the ionization in the electroscopes could as well be explained by them as by photons. Thus according to Bothe and Kolhoerster the cosmic rays were not like γ-rays, but simply a shower of high speed electrons. This meant that the electrons observed at sea-level have to penetrate the entire atmosphere. Now the amount of energy which they need to be able to do this can readily be computed and comes out the enormous value of a billion electron-volts, that is, the energy which the electron acquires when it falls through a potential difference of a billion volts. This is a stupendously great energy, as one is able to realize when one remembers that it is five hundred times the voltage which it has thus far been possible to produce in the laboratory.

Bothe and Kolhoerster's experiment, though it indicated the cosmic rays to be principally high speed electrons, or more exactly, high energy charged particles, since their result would have been obtained as well by protons or heavier particles, was not considered to be conclusive evidence to this effect. A great deal of work has been done since then in attempts definitely to settle this question. What seems to be a conclusive result was announced only a few months ago.

This is the work of one of our leading American physicists, Arthur Compton. The basic idea underlying his work is that if the cosmic rays are charged particles, then their motion, as they proceed toward the earth, should be influenced by the earth's magnetic field. It is well known that moving charged particles are deviated by a magnetic field, while photons remain totally unaffected. Now the earth's magnetic field differs in strength and direction at different points of the earth's surface, being stronger and pointing more downward near the magnetic poles and becoming weaker and more horizontal near the magnetic equator. This change in direction and magnitude of the field might be expected to affect the number of particles which could reach a given locality, because some might be deviated away. The problem was worked out by Lemaître and Vallarta, with the result that if the energy of the particles is not extremely high, then in regions near the magnetic equator (which is near the geographical equator), a portion of the particles is prevented from reaching the surface of the earth. Accordingly one would expect to find that the intensity of the cosmic rays would be less in these regions, since the intensity of the radiation, as measured with an electroscope, must evidently be proportional to the number of ionizing particles which strike it in unit time. Professor Compton and a large group of co-workers have during the past year made a world-wide survey of the cosmic-ray intensity with refinement of technique and thoroughness not previously approached. They found an unmistakable decrease in the cosmic-ray intensity as they approached the magnetic equator, whether in the Eastern or the Western hemisphere. This result showed without much probability of error that the major part at least of the cosmic rays consists of charged particles, and it may be said that this is now the generally accepted view.

The nature of these charged particles is still an open question. Experiments for the purpose of finding an answer are now in progress at several laboratories in this country. Likewise is the question of where the particles originate and how they attain their enormous energies. The older theories of the origin of the rays must of course be discarded since they assumed a gamma-type radiation. The principal suggestion which has been made recently is one due to Lemaître. His theory is bound up with the problem of stellar evolution, so that it would take us too far afield to give anything but the merest outline of his theory. He first points out that there are difficulties with believing that cosmic rays are now being generated in the stars. For one thing, the sun, a typical star, it has been repeatedly shown, is not even a feeble source of the radiation. In addition the stars have atmospheres which would effectively prevent the radiation from escaping from the interior. Furthermore, there are now reasons for believing that the stars were formed by a relatively rapid process of evolution in the remote past (the so-called "fireworks" theory of stellar evolution), rather than by a slow process continuing up to the present day. As Lemaître puts it, "The last two thousand million years are slow evolution: they are the ashes and smoke of bright but very rapid fireworks." For these reasons he believes that the cosmic rays were generated during the original "fireworks" by the disintegration of super-radioactive elements which have long since all disintegrated away. These rays have been wandering around our closed universe ever since, and a small portion of them is still reaching the earth.

There are also a number of other interesting questions which require investigation. For example, we know as yet very little about the exact manner in which the radiation is absorbed. It seems probable that the future investigations in this field will lead not only to a complete understanding of the cosmic rays themselves but will also indirectly yield much new knowledge of atomic physics, particularly of the structure and properties of the nucleus.

L. M. MOTT-SMITH.

III

THE SYNTHESIS OF GALLSTONES

THE problem of the mechanism of the formation of gallstones has claimed the attention of numerous investigators from the very beginning of the art of medicine. But in spite of all the work that has been done, there is still considerable difference of opinion as to the origin of these troublesome stone-like bodies which all too frequently are deposited in the gall bladder or ducts of both man and animals. In the course of this lecture it is proposed to give an account of some recent investigations carried out by Mr. Gray and myself on the synthesis of the most common types of human gallstones. It is hoped that the results of this work will throw light on an age-old problem and will be helpful in its ultimate solution.

The modern view of the mechanism of gallstone formation is the direct outgrowth of recent developments in the science of colloid chemistry. Although the colloidal theory of gallstone formation is largely the product of recent investigations, it should be recalled that what is now termed colloidal behavior was recognized as important in producing concretions by Hippocrates, the Father of Medicine, in the fourth century B. C. and by Galen in the second century of our era. These renowned physicians of ancient Greece attributed the abnormal deposits to an accumulation of mucus which clung to the organ and served as a nucleus for the stone which subsequently formed. The first experimental evidence of the rôle which colloids may play in concrement formation was obtained in 1684 by A. von Heyde who dissolved out the crystalline material from a urinary calculus and observed a residual framework. This organic framework was recognized quite clearly by Meckel von Hemsbach as evidenced by the following quotation from his book, *Mikrogeologie,* published in 1856. "Two basic factors underlie the formation of every true gall or urinary stone; first, the presence of an organic substance, mucus, in which there may be depositions of salts; second, a suitable urinary or gall fluid to serve as the mother liquor for these sediments. The decomposable organic substance, mucus, is unquestionably necessary, because urinary salts and gall substances of themselves can yield only crystalline, pulverulent or granular precipitates and never larger pieces. Stones are formed only when an organic binder is carried down too."

While the presence of a colloidal organic binding material resulting from an inflammatory process has been definitely established as essential for the formation of certain types of concretions,[1] it was demonstrated almost a quarter of a century ago by Aschoff and Bacmeister[2] and by Schade[3] that both gall and urinary calculi may form under suitable conditions without inflammation as a result of infection.

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[1] Pfeiffer: *5th Cong. Int. Med.,* Wiesbaden (1886); Posner: *Arch. klin. Med.,* **5,** (1885); **16** (1889); Naunyn: *Klinik der Cholelithiasis,* Leipzig (1892); Gilbert and Dominici: *Compt. rend. soc. biol.,* **28,** 1033 (1893); Moritz: *14th Cong. Int. Med.,* Wiesbaden (1896); Gilbert: *Arch. gén. de Méd.,* **2,** 257 (1898); Gilbert and Fournier: *Presse Med.,* **7,** 259 (1898); Mignot: *Arch. gén. de Med.,* **129,** 263 (1898); Schrieber: *Virchow's Archiv,* **153,** 147 (1898); Cushing: *Bull. Johns Hopkins Hosp.,* **10,** 166 (1899).

[2] *Cholelithiasis* (1909); *Lectures on Pathology,* 206 (1924); Kleinschmidt: *Die Harnsteine* (1911).

[3] *Münch. med. Wochenschr.,* Nos. 1 and 2 (1909); *Kolloid-Z.,* **4,** 175, 261 (1909); *Kolloid-Beihefte,* **1,** 371 (1910); Alexander's *Colloid Chemistry,* **2,** 801 (1928); cf., also, Boysen: *Über die Struktür und Pathogenese der Gallensteine* (1909).

COMPOSITION OF THE BILE

Since the crystalline constituents of gallstones are derived from the bile, consideration will be given first of all to the nature and composition of this secretion.

The bile or gall is a viscid, yellowish or greenish liquid consisting of solids dissolved or dispersed in water. Since the secretion is concentrated in the gall bladder, gall bladder bile always contains more of the solid constituents than common duct bile, the concentration increasing with the length of time of storage. Rous and McMaster[1] showed that in certain cases the concentration may be increased as much as ten fold in twenty-four hours. The second and third columns of the following table give the average composition of normal human common duct and gall bladder bile, respectively, from a number of sources as reported by Rosenbloom.[2] In the last column of the table is given the manner in which the several solid constituents are held in the bile fluid.

Constituents	Percentage composition		State
	common duct	gall bladder	
Water	98	86	——
Inorganic salts NaCl, $CaCl_2$, $CuCl_2$, etc.	0.7	0.8	In molecular solution
Sodium glycocholate and taurocholate	0.9	9.1	Partly in molecular solution but chiefly as colloidal electrolytes dispersed like the soaps
Mucin and pigments	0.5	2.6	In colloidal solution
Lecithin and fat	0.3	0.8	Emulsified by the cholates
Cholesterol	0.12	0.48	Peptized by the alkali cholates; dissolved in the emulsified fat; and collected around the droplets.

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[1] *J. Exptl. Med.,* **34,** 47 (1921).

[2] *J. Biol. Chem.,* **14,** 241 (1913).

The chief inorganic salts in the bile are the chlorides of sodium, potassium, and calcium but traces of iron, copper, and zinc salts may be present.

The bile salts, sodium glycocholate and taurocholate, are the most important constituents of the bile. Like the soaps they are exceptionally good emulsifying agents and their rôle in the process of digestion is to emulsify the fats in the foods. They also retain the fatty constituents of the bile in the form of an emulsion. Their extremely bitter taste is responsible for the well known phrase, "bitter as gall."

The biliary mucin secreted by the gall bladder wall is a glucoproteid like that in the saliva. Its function may be to lubricate the bladder bile, which becomes thick and tenacious on standing and it may serve to facilitate the passage of gallstones.

The coloring matter of the bile is chiefly bilirubin, which is reddish brown, and biliverdin, an oxidation product of bilirubin, which is green. These compounds are insoluble in water but dissolve in the alkaline bile probably forming colloidal electrolytes the colloidal anions of which are colored. The calcium salts of these pigments are insoluble and are the chief constituents of the so-called "pure" calcium-pigment gallstones which are sometimes encountered.

Cholesterol was first found in gallstones and for this reason was given the name solid bile (from the Greek *chole,* bile; *stereos,* solid). It is the chief constituent of nearly all biliary concretions and is present in greater or less amount in all of them. In the pure state it is a white, light, flaky, crystalline solid insoluble in water but fairly soluble in both alcohol and fats. The form of the crystals deposited from the saturated solutions in the respective solvents is shown in Fig. 1, (A) and (B).

It is commonly stated that the cholesterol is held in the

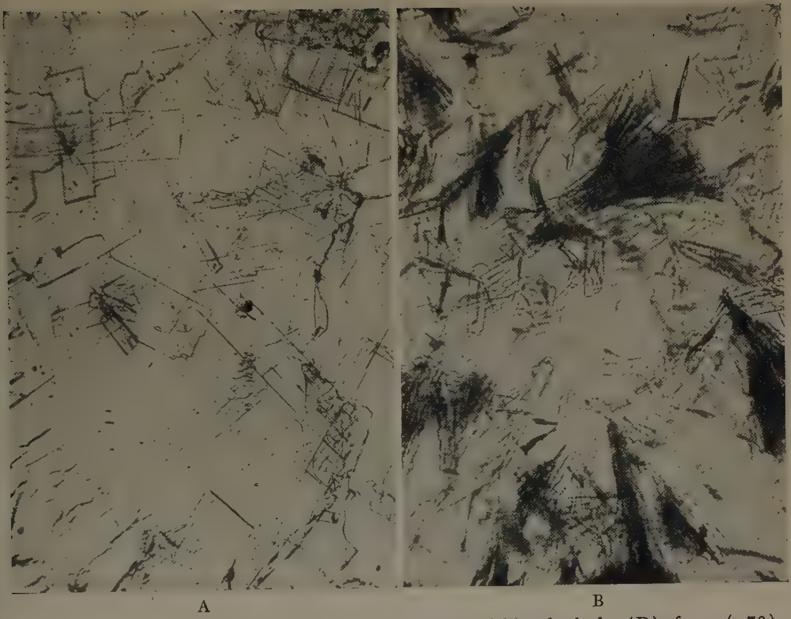

FIGURE 1. Cholesterol crystals deposited from (A) alcohol; (B) fat. (x70).

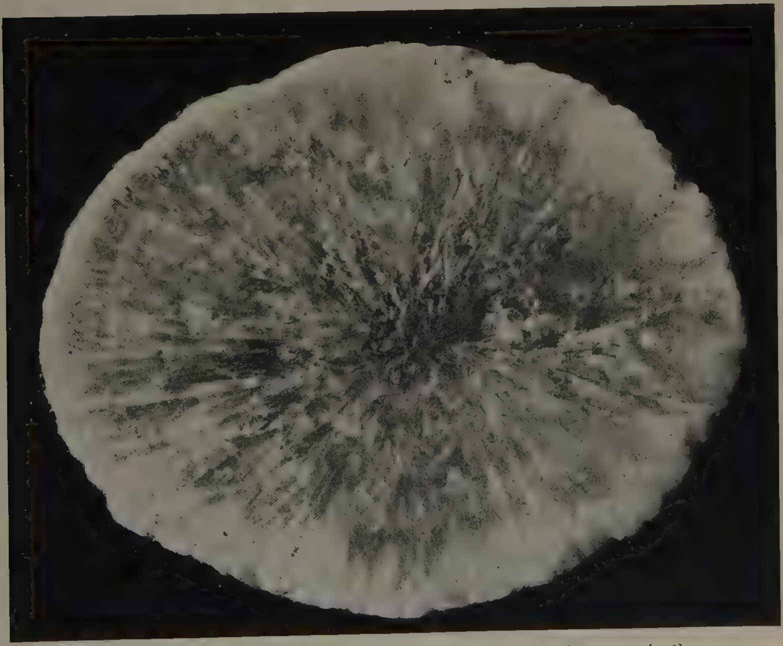

FIGURE 2. Cross-section of pure cholesterol gallstone. (x6).

dispersed state in the bile by the peptizing action of the alkali cholates. This statement we have found to be only partially correct. Fat-free cholesterol was suspended in an 8 per cent solution of sodium glycocholate and digested for several days at 37°C, the body temperature. The amount taken up corresponds to but 0.2 gram in 100 cc of solution or one part of cholesterol to forty parts of bile salt. In contrast to the relatively low peptizing action of the cholates is the marked solubility of cholesterol in fats. Thus at body temperature 100 cc of olive oil dissolves 6 grams of cholesterol. Since the bile may contain one per cent or more of fatty material it is apparent that one-third to one-half the cholesterol in normal bile is dissolved in the emulsified fat. Moreover, as we shall see, any excess cholesterol tends to concentrate around the fat droplets.

GALLSTONES FORMED WITHOUT INFECTION

Stones formed in the gall bladder without the coexistence of inflammation resulting from infection are usually designated as "pure" stones, as for example, "pure cholesterol stones" or "pure calcium pigment stones." The cholesterol stones, which are much the more common, will be taken as the example of this type. Since such stones always occur singly, Meckel von Hemsbach[1] called them "cholesterol solitaires." They consist largely of cholesterol, although fat and small amounts of alkali and calcium cholates, and bile pigments, are usually present. Fig. 2 shows a cross section of a stone which was nearly pure cholesterol. The specimen was white throughout hence was free from bile pigments. A portion of the specimen was found to be almost completely soluble in ether, indicating that it was largely cholesterol and fat.

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[1] *Mikrogeologie* (1856).

The incidence of pure cholesterol stones is believed by Aschoff[1] to result from a disturbed metabolism which gives an abnormally high content of cholesterol in the blood and subsequently in the bile. According to Dostel and Andrews[2] a survey of the experimental evidence does not support this view; on the contrary, it shows the absence of any connection between the cholesterol content of blood and bile. Quite recently, however, Wilkie and Doubilet[3] at McGill have made some striking observations which support Aschoff's theory. Thus it was shown that in normal animals with the cystic duct tied, cholesterol passes from the blood through the mucosa of the gall bladder into the bile provided the cholesterol concentration of the bile is lower than that of the blood, whereas cholesterol passes from the bile through the gall bladder into the blood stream provided the cholesterol concentration of the bile is higher than that of the blood. Moreover, the amount as well as the direction of passage of the cholesterol appears to depend on the blood-bile cholesterol ratio.

In contrast to Aschoff's theory, Naunyn[4] attributes the presence of excess cholesterol which may lead to stone formation in the gall bladder to the disintegration of gall bladder epithelium or to the direct secretion of cholesterol by the gall bladder mucosa. This view has been pretty largely disproved and has been abandoned by most pathologists. Recently, however, it has been revived by Elman and Graham[5] to account for the presence of cholesterol crystals in the walls of the gall bladder. While this pathological condition called cholesterosis or "strawberry" gall bladder is

[1] *Lectures on Pathology*, 206 (1924).

[2] *Arch. Surgery,* **26,** 258 (1933).

[3] *Arch. Surgery,* **26,** 110 (1933).

[4] *Klinik der Cholelithiasis* (1892).

[5] *Arch. Surgery,* **24,** 14 (1932).

well known, it does not follow that the crystals deposited in the gall bladder mucosa are secreted by the mucosa.

On one point everybody is agreed: whatever the source of the excess cholesterol, a condition must arise which causes precipitation of the compound or no stone can form. During stasis, Aschoff visualizes the precipitation from a hypercholestolated bile about some nucleus, ultimately leading to the formation of a gallstone. While this step is necessary, pathologists have been slow to recognize that precipitation is in itself altogether inadequate to account for the binding together of the crystalline particles into a concretion. Schade[1] realized the necessity of accounting for the collecting together of the precipitated cholesterol into a coherent mass and proposes the following mechanism:

> Bile always contains, in addition to cholesterol, small quantities of fat dissolved in its cholate. Now in stasis of the bile, as the experience of the surgeon and the pathologist proves, the concentration of the cholate is gradually diminished by autolysis and resorption until finally a water-clear, almost cholate-free fluid is left; but the cholesterol remains in undiminished quantity and is ultimately in excess. The increasing impoverishment of the bile in cholate content, compels small quantities of cholesterol to separate out from time to time. But owing to the presence of fat it is guttulate separation which occurs, and since in such simple stasis, foreign substances are lacking, there is nothing to prevent the aggregation of the droplets.

While Schade's proposed mechanism possesses elements of value it is based on certain misconceptions which render it inadequate. In the first place, it is taken for granted that the alkali cholates can hold large amounts of cholesterol in the dispersed state; but, as we have seen, it requires in the neighborhood of forty parts of cholate to disperse one part of cholesterol. In the next place it is assumed that during stasis the cholates gradually disappear allowing the cholesterol to precipitate. But Rous and McMaster[2] and more recently Andrews, Dostal, Goff, and Hrdina[1] have demonstrated conclusively that stasis alone does not necessarily alter the bile salt-cholesterol ratio in the gall bladder. The introduction of some other factor such as bacterial infection or chemical irritation, say by pancreatic juice, is necessary for resorption of the bile salts to take place. But inflammation from infection, or, indeed, anything more than a relatively mild chemical inflammation, is not essential for the formation of pure cholesterol solitaires since gall bladders in which they are found usually show no signs of inflammation and the pathological results of infection are absent. Moreover, in the presence of infection, stones of a distinctly different type are formed.

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[1] Alexander's *Colloid Chemistry,* **2,** 801 (1928).

[2] *J. Exptl. Med.,* **34,** 47 (1921).

Finally, emphasis is laid on the importance of the presence of excess fat; but, as we have seen, cholesterol is quite soluble in fat and an excess of the latter would tend to prevent rather than favor the formation of gallstones.

The following experiments appear to throw considerable light on the mechanism by which precipitated cholesterol may be collected into a unified coherent mass.

1. A drop of olive oil was shaken with 10 cc of a 6 per cent solution of sodium glycocholate. A stable emulsion was formed in which the droplets vary in size from extremely minute to fairly coarse. Fig. 3 shows the appearance of a portion of this emulsion magnified seventy times. The emulsion is quite stable but tends to "cream" on standing giving an upper layer that is relatively richer in fat than the lower layer.

2. A drop or two of olive oil saturated with cholesterol at 50° was added to 10 cc of the sodium glycocholate solution at 25° and the mixture shaken vigorously. An emulsion was again formed but this time there was present an

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[1] *Ann. Surgery,* **96,** 615 (1932).

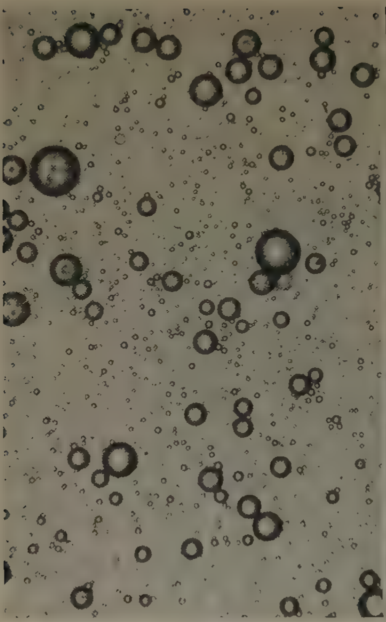

FIGURE 3. Fat emulsified by sodium glycocholate. (x70).

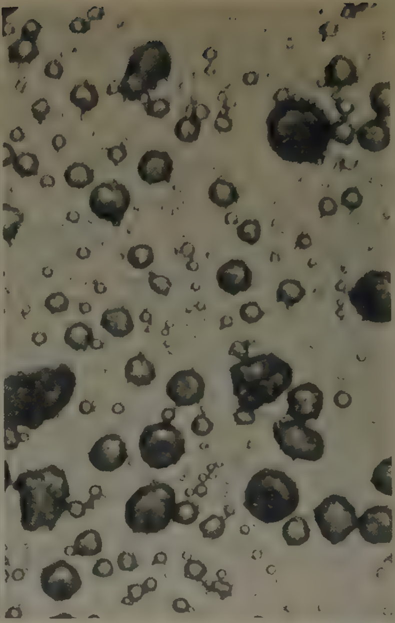

FIGURE 4. Emulsified fat droplets surrounded by cholesterol. (x70).

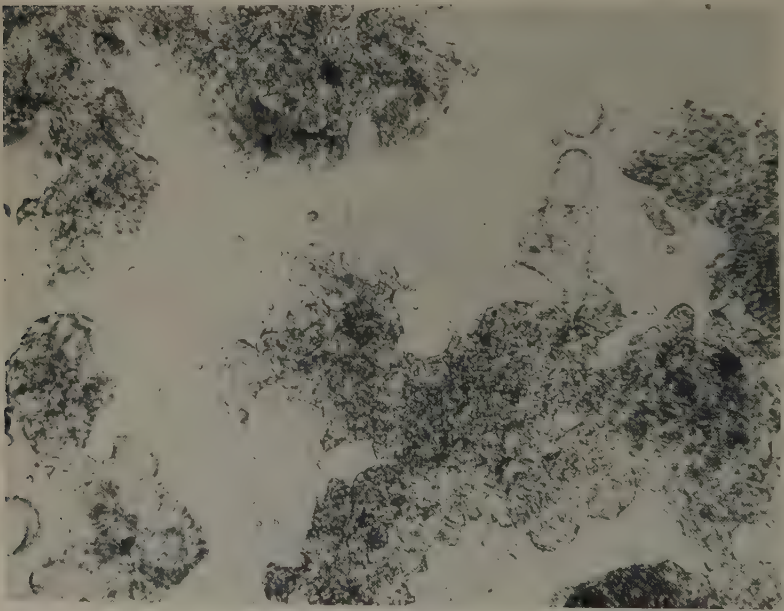

FIGURE 5A. Growth of cholesterol crystals in a cholesterol-fat clump. Original clump. (x70).

amount of free cholesterol in excess of the amount required to saturate the fat at 25°. A small portion of this excess cholesterol is peptized by the alkali cholate and the remainder concentrates on the surface of the droplets of emulsified fat. This is shown very clearly in Fig. 4. It is interesting to note that under these conditions the fat droplets have an "armor plate" of cholesterol as evidenced by the fuzzy appearance of the edges of most of the fat droplets and by the distortion in shape of many of them. It is apparent that cholesterol has a marked tendency to collect at an oil-water interface. For this reason, in the bile any excess cholesterol over and above that dissolved in the bile fat and peptized by the alkali cholates, concentrates at the surface of the droplets. It thus appears that the chief rôle of the bile cholates in holding relatively large amounts of cholesterol in colloidal dispersion is as an emulsifying agent for the fats, thereby furnishing a relatively large surface on which minute particles of cholesterol are adsorbed and prevented from settling out.

3. Like most emulsions, those considered in the preceding paragraph "cream" on standing, that is, the upper portion becomes relatively richer in fat. This process is accompanied by some coalescence, especially of the larger drops, into still larger units. When the droplets are coated with a film of cholesterol there is a marked tendency to form clumps of droplets. Thus after an emulsion containing excess cholesterol has stood for a day or two, it is apparent that a considerable portion of the cholesterol has collected in an upper cloudy layer. Examination under the microscope reveals the presence of clumps of droplets coated with cholesterol so finely divided that no crystal structure is visible. A typical clump of this kind is shown in Fig. 5,A. Note the irregular shape of the clump and the white color which

is due to the minute particles of cholesterol in the oil-water interface.

4. For the formation of large cholesterol crystals from the minute particles, it is necessary for the emulsifying film of sodium glycocholate to be broken so that cholesterol can come in contact with the saturated fat droplets. Under such circumstances it would be expected that the minute particles would dissolve and reprecipitate out in larger units. There proved to be two relatively simple methods of breaking the glycocholate film on the droplets: first, add a trace of acid which converts the glycocholate to glycocholic acid which is not an emulsifying agent; or second, allow the sample to dry, thus causing the film of the hydrophilic emulsifying agent to crack.

The effect of allowing the specimen shown in Fig. 5,A to stand in the air for six hours is shown strikingly in Fig. 5,B. Note the disappearance of the minute particles of cholesterol and the formation in their stead of the fan-like, feathery crystals similar in all essential respects to those reproduced in Fig. 1,B. This process is accompanied by the release of the greater portion of the fat solvent. The phenomenon demonstrated in Fig. 5,A and B is shown in an even more striking fashion in Fig. 6, in which (A) represents the original clump and (B) and (C) the same after standing four and twenty hours, respectively. Note the relatively large size of the particles especially in (C) and that they are suspended in a drop of fat the outline of which is clearly visible.

5. It would appear obvious that the formation of a mass of interlocking crystals by the mechanism described in the previous paragraph would yield a relatively firm "stone". This was demonstrated by pouring fat supersaturated with cholesterol in glycocholate solution, emulsifying, allowing to

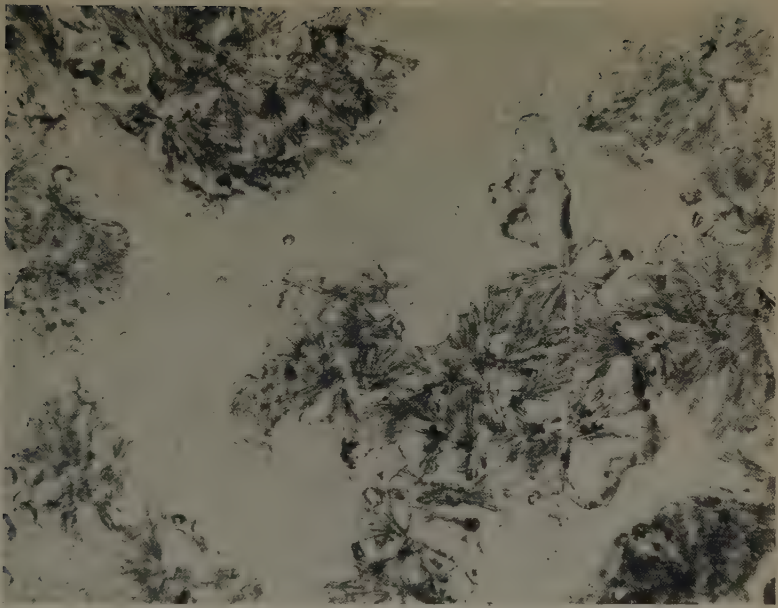

FIGURE 5B. Same as Figure 5A after 6 hours. (x70).

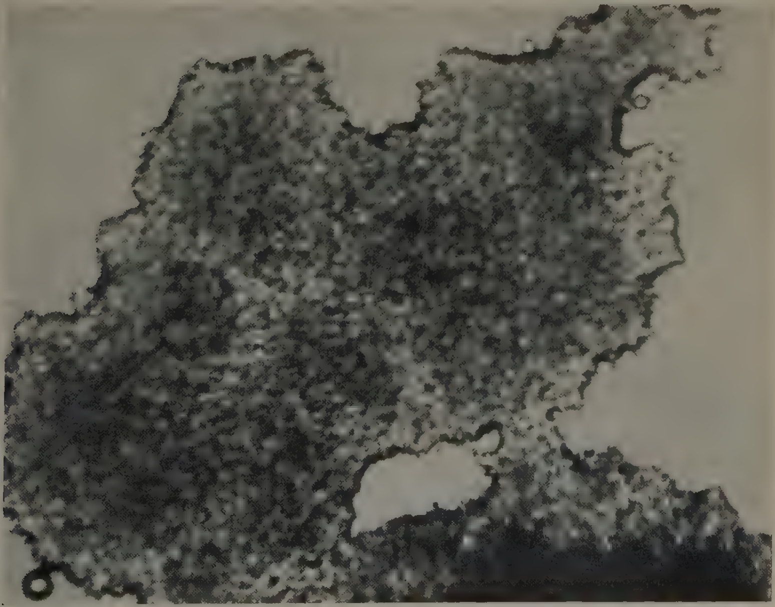

FIGURE 6A. Growth of cholesterol crystals in a cholesterol-fat clump. Original clump. (x70).

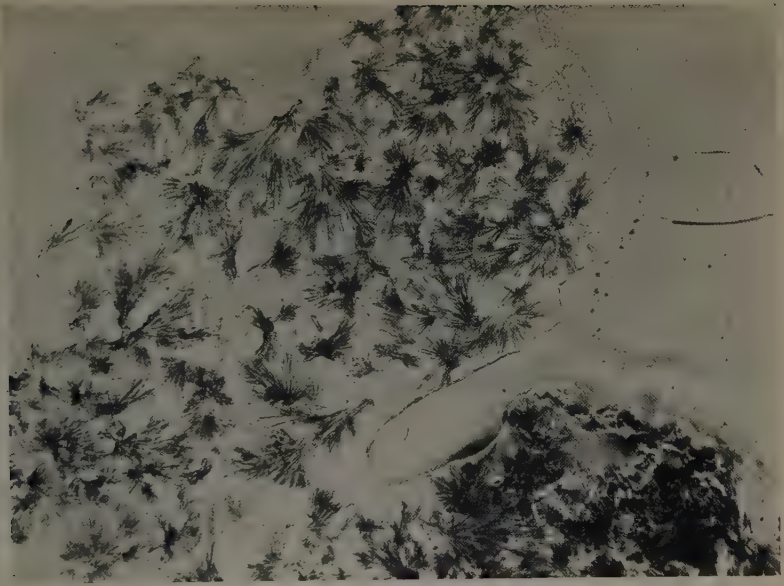

FIGURE 6B. Same as Figure 6A after 4 hours. (x70).

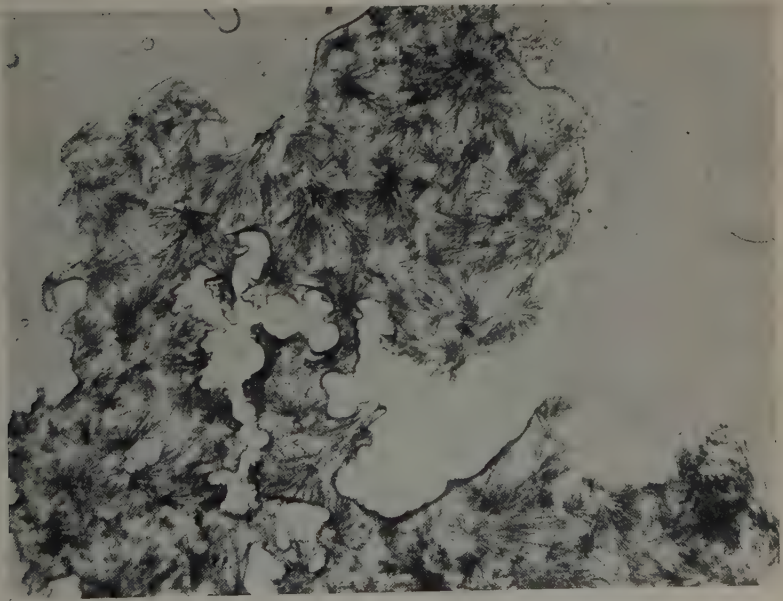

FIGURE 6C. Same as Figure 6A after 20 hours. (x70).

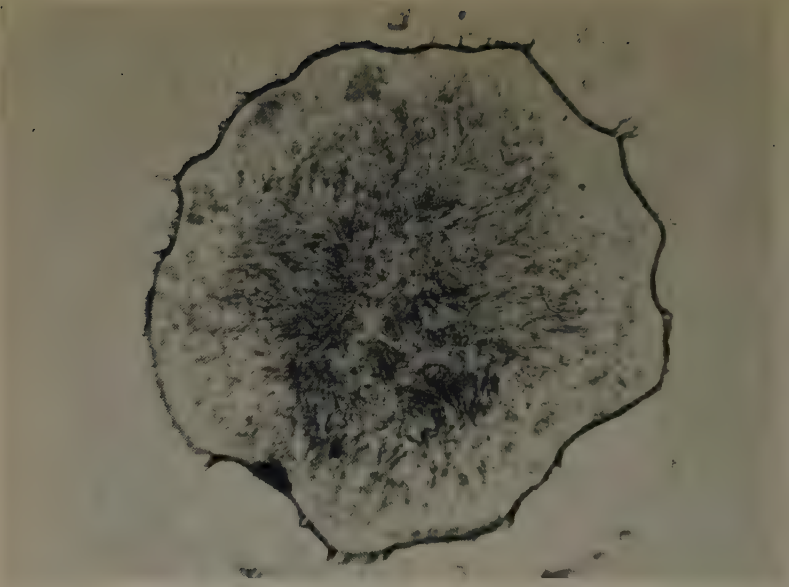

FIGURE 7. Synthetic pure cholesterol stone. (x10).

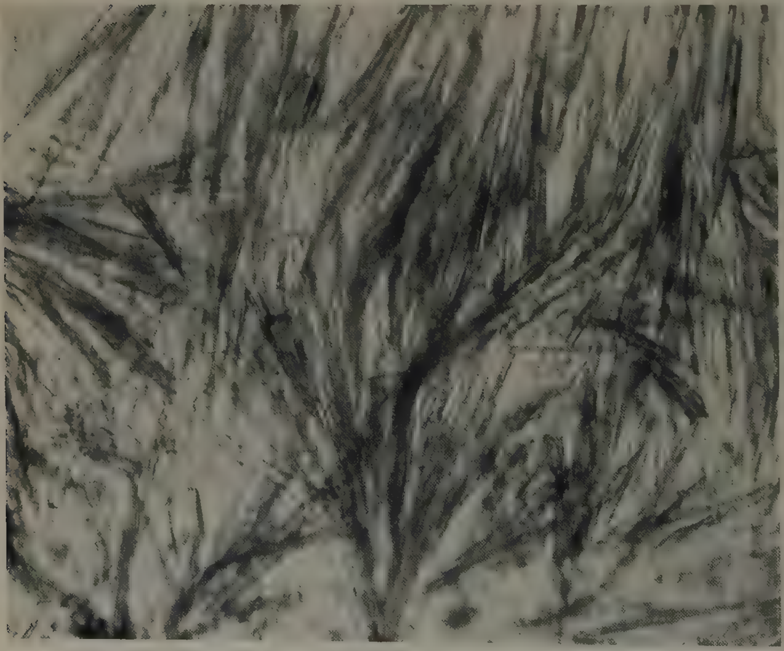

FIGURE 8. Portion of synthetic pure cholesterol stone. (x70).

stand for some time, and then separating the mass of fat and cholesterol from the remainder of the emulsion by centrifuging. After absorbing the excess fat with blotting paper, it was formed into a ball and dried. The result was a relatively hard crystalline mass, simulating the natural pure cholesterol stone in appearance, composition, and properties. To prepare a photograph, a small ball of the cholesterol mass was flattened out on a microscope slide, dried, and digested at body temperature for four weeks. The result is shown in Fig. 7. Although the magnification is only ten diameters, the radial crystalline structure characteristic of the natural stones is clearly revealed. Fig. 8 is a section of the preparation shown in Fig. 7, magnified seventy times. The higher magnification shows in a striking way how a coherent body is obtained as a result of the laying down of an interlacing mass of needle-like crystals.

In the light of the above series of experiments the mechanism of the formation of cholesterol stones in the absence of inflammation due to infection is believed to be as follows:

In bile stasis resulting from anatomical or physiological abnormalities[1] the bile collects and concentrates in the gall bladder where it may remain for a long period. During this period of stasis there may be an infiltration of cholesterol from a hypercholesterolated blood and a decrease in the amount of the alkali cholates which are responsible for retaining the fat in the form of an emulsion as well as the cholesterol in the dispersed state. In the absence of infection, a decrease in alkali cholates may result from either or both of the following causes: (1) a change in the pH of the bile from the alkaline to the acid side thereby converting the alkali salt to the insoluble glycocholic acid which is neither an emulsifying agent for fat nor a peptizing agent for cholesterol; or (2) a physiological change in the gall bladder wall which allows resorption of the alkali cholates.

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[1] Cf. Aschoff: *Lectures on Pathology,* 194 (1924).

There is no doubt that the first factor above mentioned will contribute to the precipitation of cholesterol since gall bladder bile is normally acid while hepatic duct bile is alkaline. This normal change in pH is probably accentuated in bile stasis.

In the normal gall bladder there is little or no resorption of alkali cholates. Since pure cholesterol stones are found in gall bladders that show no signs of inflammation, past or present, it follows that any resorption of cholates that leads to the formation of a pure cholesterol stone must result from a physiological derangement that does not produce histological changes. Clinical irritation that is not sufficiently severe to leave a permanent change in the tissue may be a contributing factor. Thus a reflux of pancreatic juice into the gall bladder causes cholecystitis and results in marked absorption of cholates.[1] The injection of bacteria produces a similar effect but this changes the whole picture, causing lesions and leading to a different type of stone.

The disappearance of alkali cholate either by conversion to glycocholic acid or by resorption, causes precipitation of cholesterol. This is, of course, most marked in highly hypercholesterolated bile. The excess cholesterol collects around the fat droplets which tend to coalesce as the cholate is gradually removed. Clumps of fat interspersed with cholesterol result and the process of solution of the finely divided particles and subsequent reprecipitation in large needle-like crystals, binds the mass together. The continuation of this process for a long period leads eventually to the concrement which consists of relatively large crystals of cholesterol together with a small amount of enclosed fat.

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[1] Wolfer: *Surg. Gynecol. and Obstet.*, **53**, 443 (1931); Andrews, Dostal, Goff, and Hrdina: *Ann. Surgery*, **96**, 595 (1932).

Particular attention should be called to the importance of fat in the synthesis of pure cholesterol stones. Not only does it serve as a collecting agent which brings together the particles of precipitated cholesterol but its solvent action is responsible for the growth of the interlacing crystals. Since the bile contains no solvent for cholesterol except the fat, the presence of the latter is essential in the formation of pure cholesterol stones such as those shown in Figs. 2 and 7.

GALLSTONES FORMED WITH INFECTION

The marked inflammation accompanying an infection in the bile duct or gall bladder introduces into the bile irreversibly precipitating hydrophilic colloids such as serum albumin, globulin, and fibrin. If cholesterol or calcium bile pigments separate in the presence of such colloids, there is mutual adsorption with the result that the whole is united into a coherent mass giving what is sometimes termed a colloid-crystalline stone as distinct from the pure crystalline stone considered in the last section. Since approximately two-thirds of the gallstones are of inflammatory origin[1] it follows that colloid-crystalline stones are the type most commonly found in the gall bladder.

As has been pointed out, the formation of pure cholesterol stones is probably preceded by the separation of the cholesterol and its concentration on the fat droplets followed by agglomeration and subsequent formation of an interlacing mass of crystals. A similar mechanism may obtain when inflammation resulting from infection is present but in the latter case such a mechanism is not essential since the colloidal material resulting from the inflammatory process may bind the mass firmly into a concrement. The first step, namely, the precipitation of cholesterol, is doubtless due chiefly to resorption of the alkali cholates by the inflamed gall bladder wall.[1]

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[1] Cf. Aschoff: *Lectures on Pathology,* 217 (1924).

The importance of the colloidal binding material in concrement formation is shown by dissolving out first one constituent and then the other from a colloid-crystalline stone. If the crystalline material is removed with a suitable solvent, a firm coherent skeleton of colloidal matter remains which shows the details of structure of the stone. On the other hand, if the albuminous skeleton is dissolved out by antiformin, there is complete disintegration, nothing remaining but a slimy mass of minute crystals.[2]

Since the relative amounts of the various constituents which make up gallstones of inflammatory origin may vary widely, it is obvious that the composition, appearance, and physical properties of the stone will show almost infinite variation. In a stone in which there is a relatively small amount of hydrophilic colloid, the soft irregular masses consisting largely of cholesterol, undergo solution in fat and recrystallization, ultimately giving a radial structure similar to that in the pure cholesterol stone. Adsorption of the bile pigments or their precipitation as the calcium salts[3] stains the stone to a greater or lesser degree depending on the relative amount of pigment adsorbed or thrown down. If the amount of hydrophilic colloids present in the stone is relatively large, crystal growth is inhibited and the formation of long crystals is prevented. Since the hydrophilic colloids lose water and shrink with time, stones containing a large amount of such colloids may become sufficiently friable that they fall to pieces. In other cases the aging may make radial rifts leading out from the center leaving an irregular hollow space which fills with liquid.

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[1] Cf. Andrews, Dostal, Goff, and Hrdina: *Ann. Surgery,* **96,** 619 (1932).

[2] Schade: *Med. Klinik,* No. 15 (1911).

[3] The so-called calcium salt of the bile pigments is probably an adsorption complex of indefinite composition.

The most common form of gallstones are the colloid-cholesterol-calcium pigment stones that are characterized by the presence of concentric rings varying in color. Such concretions are termed layered stones or "common gallstones". In these stones the kernel and the surrounding ring structure are readily distinguished. The former consists largely of albumin, calcium bilirubin, and cholesterol without the presence of a definite ring structure, while in the latter, there are a number of colored rings in crystals of cholesterol.

Unlike pure cholesterol stones, gallstones of inflammatory origin seldom or never occur singly. In rare instances there may be but two or three such stones but as a rule the number is much larger, a hundred or more, in some cases. Obviously the inflammatory process introduces numerous nuclei on which the mixture of cholesterol and hydrophilic colloids will collect. Because of the pressure of the gall bladder the stones are seldom spherical but are faceted and usually of widely varying shapes.

A pure cholesterol stone formed without symptoms of disease frequently becomes impacted in the neck of the gall bladder or the cystic duct. This can readily lead to a disturbance in the sphincter region, to reflex disturbances of bile secretion and to ascending infections of the bile duct and gall bladder. The infection may result in a loosening of the stone which returns to the inflamed gall bladder and becomes the nucleus about which is deposited a colloid-crystalline mass of hydrophilic colloids, cholesterol, and calcium bilirubin. This gives a so-called combination stone consisting of a nucleus of cholesterol not of inflammatory origin and the shell of the colloid crystalline type resulting from the inflammation due to infection. The infection following the impaction of a pure cholesterol stone may lead to a large number of colloid-crystalline concretions but there can be but one true combination stone in a given gall bladder.

The cause of the concentric rings in the so-called layered or common gallstones is usually attributed to layering as a result of variation in pathological conditions which produces alternate layers of cholesterol and calcium pigment. Schade[1] attributes the formation of a layered rather than a radiating structure to the effect of pressure which flattens out the crystals of cholesterol. This does not account for the beautiful regular formation of alternate dark and light rings. Moreover, in most stones of this type there is distinct evidence of radiating structure and in many cases this is quite marked as shown in the photographs of stones reproduced in Fig. 9.

The appearance of the concentric rings in the so-called layered stones suggests that they may originate as a result of the rhythmic banding first described by Liesegang as a result of his observations of the formation of rings of silver chromate when silver nitrate is allowed to diffuse into a gelatin jelly containing dichromate. Some examples of this Liesegang phenomenon are shown in Fig. 10,A and B. In Fig. 10,A the solution of dichromate-gelatin was poured on a glass plate and after setting to a jelly it was surrounded by a solution of silver nitrate; and in Fig. 10,B a drop of silver nitrate solution was placed in the center of a circle of dichromate-gelatin jelly.

The possibility that the rings in gallstones are not layers but rhythmic bands is an interesting one that has occurred to a number of people but has been taken seriously by few.

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[1] Alexander's *Colloid Chemistry,* **2,** 817 (1927).

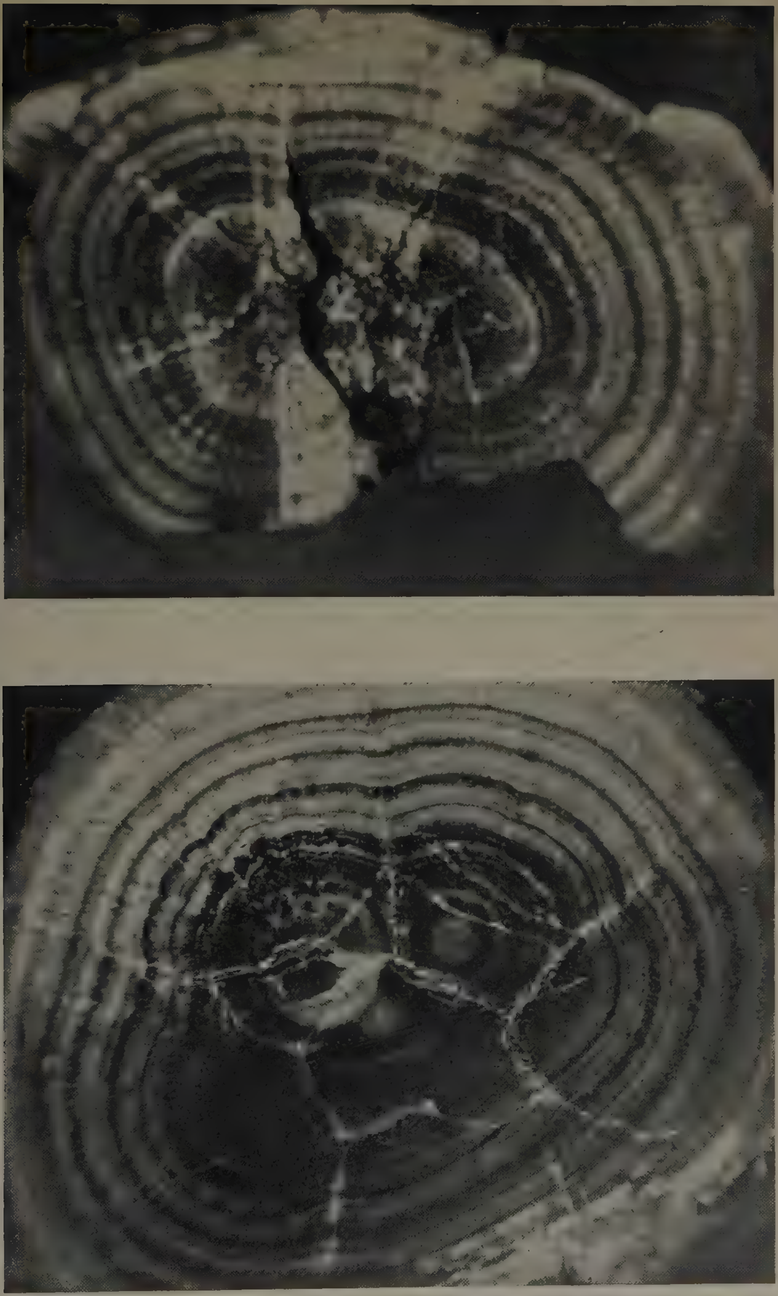

FIGURE 9. Cross-section of gallstones showing both ring and radiating structures. (x10).

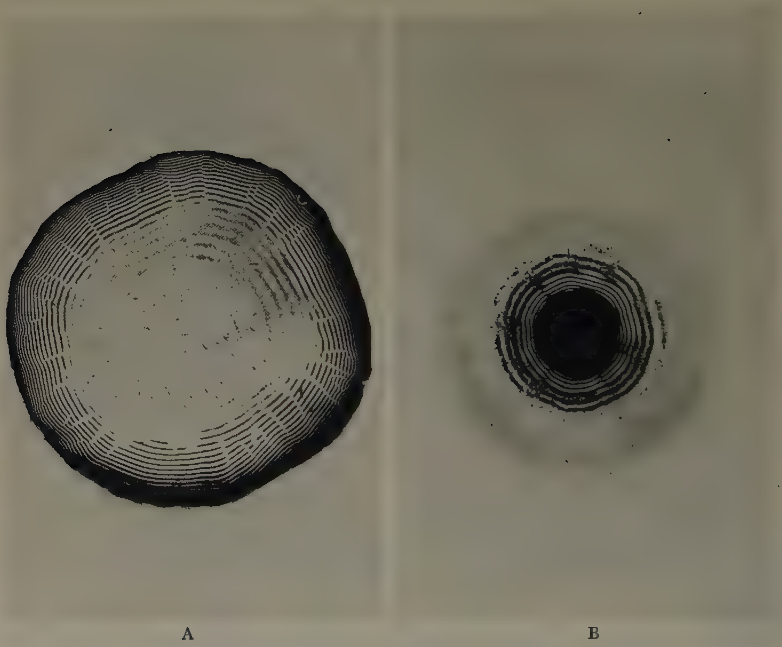

FIGURE 10. Rhythmic bands of silver chromate in gelatin formed by diffusion of silver nitrate (A) from the periphery; (B) from the center.

Schade[1] dismisses the suggestion promptly by contending that for the formation of Liesegang rings as a primary process, the diffusion must take place in a jelly which has no points of resistance to diffusion. This, he points out, does not obtain in gallstones owing to the presence of crystalline cholesterol irregularly included in the framework of hydrophilic colloids. Moreover, he rules out the formation of Liesegang rings as a secondary process, since this would give very irregular lines, which do not occur.

Sweet[2] takes the position that the concentric rings are due to the Liesegang phenomenon. He gets around the difficulty confronting Schade by postulating that the cholesterol forms a gel containing calcium into which the bile pigments such as bilirubin can diffuse giving rhythmic bands of calcium bilirubin just as silver nitrate diffuses into dichromate-gelatin jelly and gives rhythmic bands of silver chromate.

A consideration of the gallstone-bile system reveals, however, a marked difference between it and the gelatin-electrolyte system of Liesegang. In the first place, the gallstone is probably not a true jelly at any stage of its history, as assumed by Sweet. And if it did possess a true jelly structure like that of gelatin, rhythmic bands could not form as a result of diffusion since the bile pigments are in colloidal solution and so diffuse but little if at all. Schade's objection to the banding theory on the ground that rhythmic precipitation takes place only in a jelly does not hold, since the phenomenon manifests itself not only by diffusion into jellies but also into relatively non-uniform amorphous and crystalline masses. Accordingly, it is altogether possible that the precipitation of crystalline cholesterol in the presence of hydrophilic colloids will, under certain conditions, give a mass into which the colloidal pigments can diffuse and by interacting with calcium salts carried down with the cholesterol, precipitate colored rhythmic bands. In other words, the very fact that cholesterol is definitely crystalline may be the determining factor in producing rhythmic bands therein, since a mass of small crystals would allow the interdiffusion of the colloidal bile pigments.

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[1] Alexander's *Colloid Chemistry,* **2,** 830 (1928).

[2] *Colloid Symposium Monograph,* **8,** 249 (1930).

If this is a true statement of the case it should be possible to simulate the conditions sufficiently closely that rhythmic bands of calcium bile pigments will be formed in a mass of precipitated cholesterol containing calcium salts. This has actually been accomplished as will be described in the following paragraphs.

1. To show that rhythmic banding will take place in a mass of cholesterol crystals the following experiments were carried out. One gram of gelatin was dissolved in 100 cc of water containing 0.1 gram of potassium chromate and heated to 70°. Into this solution was poured rapidly 25 cc of a hot alcoholic solution of cholesterol containing 2 grams of the pure compound. The cholesterol precipitated immediately in the form of minute crystals. These were matted firmly and uniformly in the bottom of a test tube by centrifuging and the supernatant solution was poured off. The precipitate was then covered with an 8 per cent solution of silver nitrate. Upon standing, the familiar rhythmic bands of silver chromate were formed.

The above procedure was repeated keeping all the factors constant except the amount of gelatin in the solution into which the alcoholic cholesterol was poured. The gelatin solutions contained 0.75, 0.50, 0.25, and 0.05 gram, respectively, in 100 cc. In every case rhythmic bands were formed. With decreasing amounts of gelatin the bands were broader, less distinct, and further apart. When no gelatin was used, bands were not formed, but crystals of silver chromate were scattered irregularly throughout the mass.

Portions of the precipitate thrown down in the presence of a small amount of gelatin when placed on a watch glass and surrounded with silver nitrate gave rhythmic rings similar to those obtained by diffusion in gelatin.

Since bands of silver chromate in cholesterol are formed in the presence of such minute amounts of gelatin, it is obvious that the rhythmic precipitation is not taking place in a gelatin jelly. The gelatin merely serves to inhibit the growth of the cholesterol crystals and so to give a mass of minute crystals in which the diffusion phenomenon can take place under such conditions that rhythmic bands or rings result.

2. Solutions of bile pigment were prepared in the following way. Twenty-five grams of finely powdered human gallstones were extracted in a Soxhlet tube with 200 cc of ether for two days to remove cholesterol and fat. The residue was dried, washed with hot water, then with 10 per cent acetic acid and finally with water. This residue was dried and ground in small portions with two-normal sodium hydroxide and the filtered solution was used in the experiments. When a portion of the highly colored solution was subjected to dialysis in a cellophane bag, the color did not diffuse, showing that it was in the colloidal state just as it is in the bile fluid. The addition of a dilute solution of calcium nitrate did not result in immediate precipitation of the calcium-pigment complex, but, upon standing, a precipitate settled out which varied in color from reddish brown to olive green, depending upon the degree of oxidation of the pigment.

Although the colloidal bile pigments do not diffuse through gelatinous membranes, it seemed not unlikely, in the light of the above experiments with silver chromate, that a suitably precipitated mass of cholesterol crystals containing calcium would serve as a medium into which the colloidal pigments would diffuse to form rhythmic bands, thus simulating the process which probably takes place in nature. This hypothesis was confirmed by the following method of procedure. Into 50 cc of a solution containing 0.5 gram of gelatin and 0.5 gram of calcium nitrate at 70° was poured 12.5 cc of a hot alcoholic solution of cholesterol containing 1 gram of the pure compound. After prolonged centrifuging the supernatant solution was removed from the mass of precipitate and portions of the latter were placed on a microscope slide and surrounded by the solution of bile pigments. The specimens were placed in a desiccator containing an ammonia solution to prevent their drying out and to minimize the oxidation of bilirubin to biliverdin. After standing over night rhythmic rings resulted as shown by the photographs reproduced in Figs. 11 and 12. In Fig. 12 the effect of the shape of the mass on the form of the bands is clearly shown. In order to secure a plane surface to photograph, in some cases a cover glass was pressed down gently on top of the specimen flattening out the high places.

A comparison of the synthetic preparations with the natural gallstones reveals a marked similarity in appearance which indicates that rhythmic banding plays a rôle in the formation of the natural stones just as it does in the synthetic ones.

3. The objection may be raised that there is no gelatin in natural gallstones. The answer is that the action of gelatin is not specific. It is only necessary that a protective colloid be present to inhibit the growth of the cholesterol crystals and to serve as a kind of binder. Albumin and fibrin which do occur in natural gallstones may be substituted for gelatin in the synthesis of banded stones. The specimens shown in Fig. 13 were prepared in the same way as those in Figs. 11

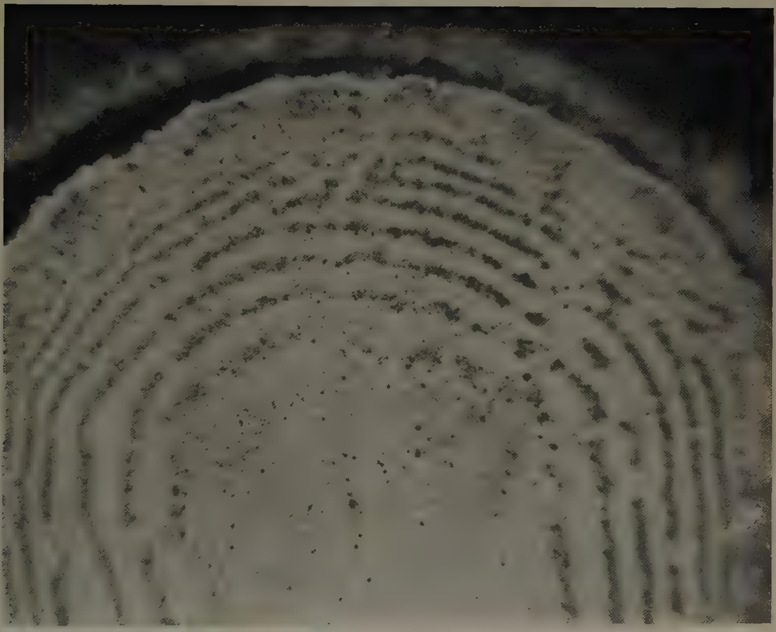

FIGURE 11. Synthetic cholesterol-calcium-pigment gallstone showing rhythmic banding. (x10).

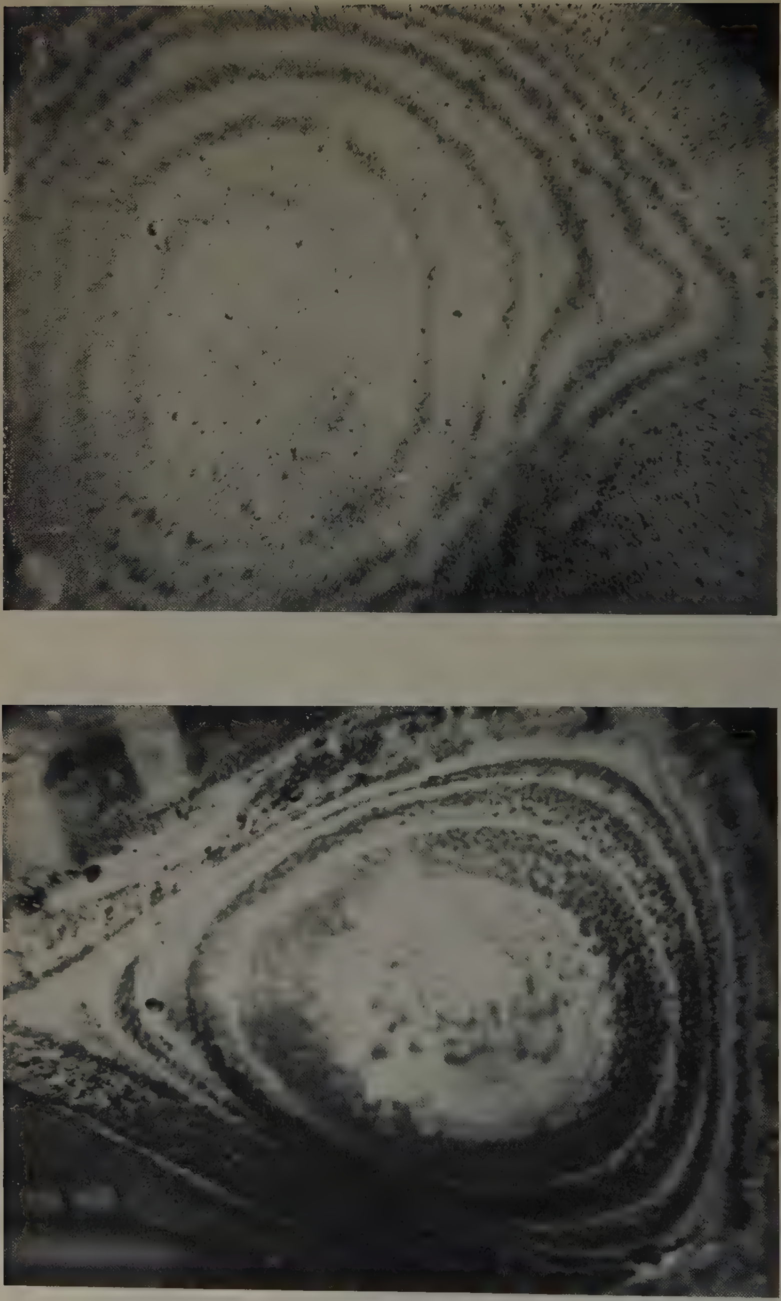

Figure 12. Synthetic cholesterol-calcium-pigment gallstones showing how the shape of the mass influences the form of the bands. (x10).

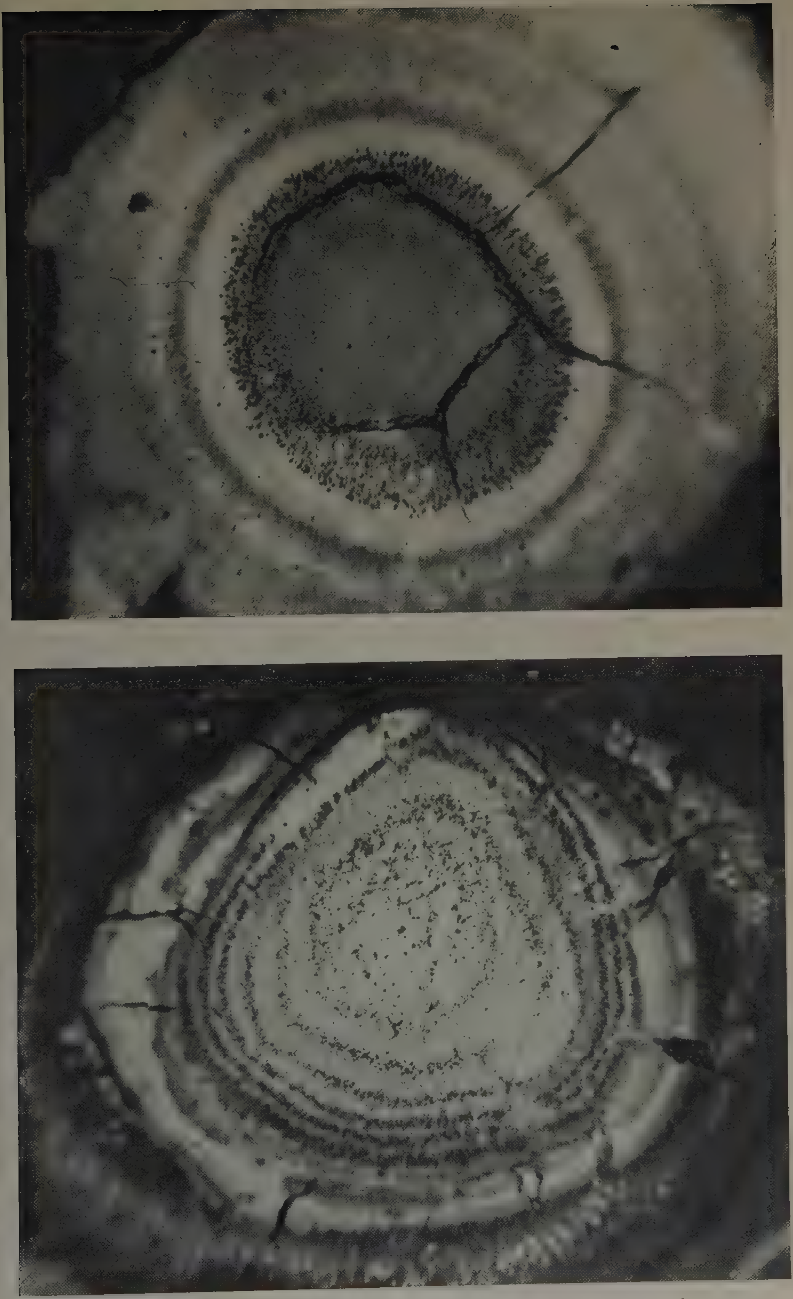

FIGURE 13. Synthetic cholesterol-calcium-pigment stones formed in the presence of a small amount of fibrin. (x10).

and 12, using, instead of gelatin, 50 cc of water in which was peptized 0.1 to 0.2 gram of fibrin.

From a survey of the conditions which result in the formation of the so-called "layered" stones and the experimental results given above, it would appear that the formation of such concretions is favored or initiated by inflammation, which yields irreversibly precipitated protein materials, such as fibrin and albumin. Pathologic changes bring about the precipitation of the cholesterol, carrying calcium with it, the nature of the precipitate depending upon the amount of hydrophilic colloid present. Into this mass the colloidally dispersed bile pigments diffuse and are precipitated in the form of rhythmic bands. The structure and arrangement of the bands is influenced by the shape of the mass, its density due to the pressure of other stones, and by variations in the composition of the bile fluid. After the bands are formed the structure may be invaded by radial crystallization of the cholesterol, cracks may develop, further deposition of the cholesterol may occur, or the stone may undergo alteration in other ways, producing the wide variety of forms which are found in gall bladder disease.

HARRY B. WEISER

IV

THE CHEMISTRY OF NARCOSIS

NARCISSUS, in Greek mythology, was the son of the river god, Cephissus, and the nymph, Leiriope. He was distinguished for his great beauty, and it was prophesied he would enjoy a long life provided he never looked upon his own features. However, he drew upon himself the vengeance of the gods by rejecting the love of the nymph, Echo; and Nemesis caused him to see his features reflected from the waters of a fountain. He fell madly in love with his own image and soon pined away. The flower that now bears his name grew up on the spot where he died. The narcissus is as interesting medically as it is mythologically because if parts of the flower are taken internally they will cause a numbness, or loss of sensation; this state is known as narcosis, and any agent that will cause it is spoken of as a narcotic. Anaesthesia and anaesthetics are more modern words that express these ideas. The use of the narcissus, as well as many other plants, for the production of narcosis, has been known for a very long time.

The history of the development of anaesthesia is an interesting record of the progress of the human race to liberate itself from Nature's lavish gift of pain. Paleopathology supplies us with an abundance of evidence that broken bones, injuries, diseases, infections, surgical operations, wounds, in fact, anything that could contribute to the production of pain was well known from the beginning of mankind. It is interesting to look back over these thousands of years and examine the attempts of mankind to alleviate the suffering associated with these conditions. We can distinguish two periods in the development of narcotics or anaesthetics: first, the Egyptian, or ancient forms, and second, the American, or modern type.

The anaesthesia of antiquity as employed by the Egyptian surgeons was fully described by Pliny. This celebrated naturalist stated that the stone of Memphis, when powdered and mixed with vinegar, would anaesthetize the region upon which it was applied to such an extent that a minor operation could be performed without pain. Dioscorides also refers to the same fact, and describes the stone of Memphis as being about the size of a talent and greasy to the touch. Modern writers have identified this marvelous stone of Memphis as calcium carbonate, or ordinary marble, and explain the anaesthetic effect as due to the action of the carbon dioxide which is produced when the substance is treated with dilute acids such as vinegar.

The use of such soporifics as opium, Indian hemp, and the mandrake was well known to the Egyptians, Greeks, and Romans at an early date. The mandrake, which is related to the potato family, has been known from remote antiquity; it is mentioned in the Bible that Rachel sought mandrakes of Leah (Genesis XXX 14-16). The mandrake has been the subject of many legends concerning the human shape of the root of the plant and of its frightful shrieks when uprooted. In early English and German folklore it was regarded as fatal to hear these terrible shrieks, so they gathered the plant by hitching a dog to it, being very careful to plug their own ears with pitch and to blow loudly upon a horn in order to drown the cries of the plant when it was pulled up. Shakespeare, more than once, alludes to this interesting plant, as when Banquo, in Macbeth, says: "Or have we eaten of the insane root that takes the reason prisoner?" The notion that the plant shrieked when uprooted is alluded to in Romeo and Juliet,

> And shrieks like mandrakes' torn out of the earth,
> That living mortals hearing them run mad.

The mandrake, often growing like the lower limbs of man, was supposed to have other virtues, and was highly prized for love philtres.

The second period in the development of surgical anaesthesia took place in America and was initiated by an accident that occurred in 1839 at an "ether frolic" at Anderson, South Carolina. At that time ether was a well known substance, and it was also well known that when administered in small amounts it would cause intoxication. Ether frolics were very common, particularly among the medical students, and even "ether addicts" were known. At this particular ether frolic, however, several over-enthusiastic young men forced a colored boy to inhale a considerable amount of ether; the subject did not become intoxicated, but fell over unconscious. He remained in this state for an hour or more, showing no subsequent ill effects upon his recovery. The idea at once suggested itself that this condition would be valuable in surgery. Dr. C. W. Long, of Jefferson, Georgia, was informed of the experiments, and in 1842 he administered ether to James Venable and removed a tumor from the patient's neck. It is interesting to note that the bill for this exceptional operation is still preserved, and it shows that the ether with the operation cost two dollars. Several years later ether anaesthesia was rediscovered and was thoroughly tested at the Massachusetts General Hospital, and a few years after this came into general use all over the civilized world.

The development of our knowledge concerning anaesthesia has been rather slow; in spite of the antiquity of the subject there is still considerable mystery surrounding the mechanism of narcosis. Several theories have been proposed to explain how narcotics cause the loss of sensation in a tissue, but they are, in general, rather restricted.

One of the theories that was advanced to explain the effect of narcotics was the theory of Verworn. Verworn studied the oxygen metabolism of various tissues while they were under the influence of narcotics, and his work showed that during anaesthesia there was a decrease in oxygen consumption. The hypothesis was then advanced that this disturbance was the cause of anaesthesia. This theory is very often referred to as the "suffocation" or "asphyxiation" theory, but it should be pointed out that the asphyxiated state does not occur by excluding oxygen from the cell but arises through the inhibition of the oxidation process by the narcotic.

There are two rather serious objections that have been raised against this theory; the first is that the decrease in oxygen consumption does not, in every case, run parallel to the various stages of narcosis, and furthermore it varies from narcotic to narcotic. The second objection is more fundamental, if the decrease in oxygen consumption is the cause of anaesthesia then it should be impossible to anaesthetize an organism that does not normally use oxygen to maintain its life functions. This experiment was tried on the intestinal worm, Ascaris, which does not require oxygen, and it was found that this organism could be easily anaesthetized. As a matter of fact it is now known that the anaerobic forms of life can be narcotized with the same ease as the aerobic; this shows that the decrease in oxidation is not essential for the production of narcosis.

The Meyer and Overton theory of narcosis is based upon the fact that narcotics are soluble in lipoids or fats, and that the strength of their action is related to the partition ratio as measured between fat and water. Meyer formulated the theory in the following way:

> (a) All chemically indifferent substances which are solvents for fats and similar bodies, must exert a narcotic action upon living protoplasm, in so far as they can diffuse therein.
>
> (b) The effect must manifest itself first, and most strongly, in those cells in whose chemical structures these fatty or lipoid substances predominate and presumably are the essential carriers of the cell function, namely, in the nerve cells.
>
> (c) The relative efficiency of such narcotic agents must be dependent upon their mechanical affinity for lipoid substances, on the one hand, and for the remaining body constituents, i. e., principally water, on the other hand. It is dependent, therefore, upon the partition coefficient which determines their distribution in a mixture of water and lipoid substance.

There are a number of serious objections to this theory. Experiments indicate that when a nervous tissue takes up a drug it does not do so by simple solution but by colloidal adsorption. Furthermore, the distribution of the narcotic within the body does not run parallel to the lipoid content of the various tissues, thus the grey substance of the brain contains 8.5% lipoid and the white matter 16%, yet narcosis starts sooner in the grey matter and is stronger than in the white matter. It is well known that the distribution coefficient will vary with the temperature, and experiments have been made to see if there is any parallelism with the change in strength of the narcotic at various temperatures; the results indicate that there is no definite relationship between the partition coefficient and degree of narcosis. Optically isomeric drugs offer a very interesting test of this theory. The optical antipodes have the same chemical structure and identical solubilities and distribution coefficients, consequently the Meyer and Overton theory would predict that they would be of equal physiological activity. However, actual experience shows that in numerous cases one isomer is many times more active than the other. The Meyer and Overton theory thus, is clearly not in agreement with the facts and consequently can no longer be seriously considered.

The theory of narcosis proposed by Traube is in many respects similar to that proposed by Meyer and Overton. The theory merely points out the parallelism between the depression of the surface tension of water by a narcotic and its strength as a narcotic. This theory has the same inherent weakness as the Meyer-Overton theory in that it only associates the physiological activity of a substance with some physical property and does not offer an adequate explanation of the mechanism by which the drug exerts its effect. Moreover, all narcotic substances do not necessarily depress the surface tension of water; magnesium sulfate behaves as a mild narcotic, yet causes an increase in surface tension. Chloroform has a negligible effect on surface tension, nevertheless it is a good narcotic. The same situation is true also of hydrocarbons and many of their halogen derivatives. One must conclude therefore, that Traube's relationship is not fundamental.

Narcosis, in its broader aspects, offers several problems that are entirely out of the scope of the theories mentioned above. For example, one can narcotize a tissue by heating or cooling it sufficiently; this would be quite unexpected on the basis of the theories already discussed. Furthermore, narcosis can be produced mechanically, as by a sharp blow, by means of an electrical current, and finally by the mere injection of distilled water.

The only theory proposed up to the present time that has any possibility of covering the many phases of narcosis was suggested in 1860 by Binz and developed later by Claude Bernard into many of its logical conclusions. This theory postulates that narcosis is caused by the mild agglomeration of the protoplasm of the nerves or tissue, and furthermore, that upon removal of the narcotic the agglomerated material will break up and be redispersed to the normal state. If the material is so strongly coagulated that the redispersion will not take place, then death occurs, and the effect of the narcotic is spoken of as "toxic". Two objections have been raised against this theory, the first is that the narcotizing concentration is much lower than the agglomerating concentration, and secondly, if the agglomeration took place it would not be reversible; both objections are based upon medical philosophy and are not the results of experiments.

The most convincing manner in which this question can be investigated would be to examine the colloids of a living cell in its normal environment under the ultra-microscope and observe what takes place when the organism is exposed to a narcotic. This experiment was carried out with yeast cells; a young vigorous culture was exposed to chloroform and placed under the ultramicroscope. At first nothing happens, after about ten minutes the Brownian movement is noticed to be decreased, and a few minutes later small aggregates of the colloids are seen. The coagulation now goes much faster, and in a few minutes, a light, but very pronounced flocculation occurs. If the material is now washed free of the narcotic and again examined under the ultramicroscope it is observed that the larger agglomerates break up, and after a short time the colloidal material is dispersed again to its original state. When the cells are treated with some toxic agent, as bichloride of mercury, the agglomeration is rapid and quite irreversible, thus illustrating the colloidal aspect of toxic action. The experimental facts, therefore, are in agreement with the theory.

It is a far fetched analogy between the narcosis of yeast cells and that of the higher organisms, and an analysis of the relation of coagulation to narcosis is more difficult in the higher forms of life, yet the evidence is clear cut, and indicates that coagulation and narcosis proceed hand in hand. The material in nerves that is undergoing the agglomeration is believed to be proteins. Now some of the colloid reactions of proteins are rather characteristic; thus if a protein sol is exposed to solutions of different hydrogen ion concentration there will be found to be a rather narrow band of concentrations in which it will precipitate. This region is called the "iso-electric" point of the protein. The iso-electric points of the protein of nerves and muscles have been measured and are fairly well known. Hence, it is not improbable that if nervous tissues were exposed to solutions of various hydrogen ion concentrations it would be found that regions which correspond to the iso-electric points of the proteins would also be regions of narcosis. This experiment was carried out by measuring quantitatively the irritability of a nerve when exposed to buffer solutions of different hydrogen ion concentrations. It was found that at the iso-electric points there were minima in the irritability curve which indicates that whenever coagulation of the protein occurs, there is a loss of irritability, or narcosis results.

The researches of Professor F. Marinesco, which involved the direct observation of the colloids of a living nerve cell under the ultramicroscope, also give direct evidence of the coagulating effect of narcotics. He showed that agents such as alcohol and magnesium sulfate coagulated the material within the nerve cell. Even more interesting, from the colloidal point of view, was the observation of mechanical coagulation, which was brought about by gently tapping the material. He also studied the effect of water on the nerve cells and found that it produced coagulation; it will be remembered that anaesthesia can be produced by injection of water into the tissue. Thus the idea of Binz and Claude Bernard that narcotics bring about a coagulation of the colloids of the tissue is not a vague dream but an observed reality that includes cases peculiarly difficult to account for on any other theory.

The chain of evidence that shows the relationship between narcosis and coagulation is strengthened by studies of the viscosity of cell protoplasm. When a tissue or group of cells is centrifuged and periodically examined under a microscope, one can observe and measure within the protoplasm the rate of sedimentation of the visible particles, such as fat and pigment. If the material is treated with a narcotizing agent and examined by this method it will be found that the viscosity of the protoplasm has undergone a marked change. These changes that occur in the protoplasm clearly indicate that the colloids are undergoing a coagulation. The narcotic decreases the viscosity of the material within the cell during narcosis, higher concentrations of the drug will cause the viscosity to pass through a minimum value and then rise rapidly above normal. Both changes in the viscosity are different phases of the same thing, namely, coagulation. It is well known that bio-colloids are highly hydrated; such colloids have a layer of water around the micellae that is commonly called the water sheath. The water that constitutes this sheath is not free, but is bound to the surface of the particles. In the first phase of the coagulation the narcotic is adsorbed upon the colloidal substrates and displaces the material that was previously adsorbed there. This increase in the amount of free, or unbound water will have the same effect on the viscosity of the sol as dilution, that is, a decrease. Also, according to Einstein's treatment of viscosity, the decreased volume of the particles will tend to lower the viscosity. As soon as the electrical charge on the micellae is lowered to such a value that flocculation occurs, the particles come together to form agglomerates, or chain structures, as in jellies, thus bringing about the increase in viscosity.

The investigation by this method of those peculiar cases of physical narcosis that find no explanation in other theories, such as by heat, cold, distilled water, a mechanical blow, and by electrical means, shows in every case the typical coagulation curves. Thus it seems that coagulation of the nervous protoplasm by chemical agents is only a special case of coagulation. The generalization can then be formulated that coagulating agents, irrespective of their nature, can behave as narcotics under suitable conditions.

In conclusion we can say that the chemistry of anaesthesia is the chemistry of sols, gels, displacement adsorption, coagulation, viscosity changes, peptization, adsorption, swelling, and catalysis; briefly, colloid chemistry applied to the muscles, nerves, glands, and cells of the affected tissues. The ultimate effect of a narcotic is the reversible coagulation of the cell colloids. This is preceded by a state of stimulation which depends upon the decreasing stability of the colloids before coagulation.

G. H. RICHTER.

V

SIR RONALD ROSS AND THE SIGNIFICANCE OF HIS WORK

IT WAS my pleasure in January, 1927, to be present at the unveiling of a bronze tablet on a gateway in front of the Presidency General Hospital in Calcutta, leading to the unpretentious little brick building in the hospital compound which Sir Ronald Ross used as a laboratory twenty-nine years earlier. That spot deserves to rank among the first in the world in historic interest, yet I had lived in Calcutta for almost three years and had passed that very gateway hundreds of times, without knowing of its existence. In an address made at the time, Colonel Megaw, then Director of the School of Tropical Medicine in Calcutta, remarked that it was astonishing that so few of the inhabitants of Calcutta knew of the existence of the little laboratory where one of the greatest discoveries in the history of the world was made. He added that although over twenty-eight years had passed, we had only begun to scratch the surface of the vast mine of wealth which that discovery had placed in our hands. "A prophet," said Col. Megaw, "is not without honor save in his own country. Sir Ronald's offense did not consist merely in being a prophet; he added to it by being a poet and a scientist, and so trebly earned the indifference with which his great work was received in India." This same Sir Ronald Ross, at the age of seventy-five, died at his modest home in Putney, England, barely six months ago. It is appropriate therefore that we should devote an hour here to a review of this great man's life and work, and to consideration of the importance and significance of his achievements.

The importance I have attached to Sir Ronald Ross's work may appear exaggerated to some of us who have lived all our lives in places where malaria is little more than a name. But in India alone there are estimated to be well over a million deaths a year from malaria, a greater number than was caused by the great European War in the first two years of its existence. Malaria is endemic over about one-third of the surface of the earth. Vast areas in Asia, Africa, and tropical America are scourged by it, and even large parts of Southern Europe and Southern United States suffer severely. According to a recent estimate 800,000,000 people in the world suffer from malaria. Can anyone even dimly visualize the amount of suffering and sorrow and economic loss that that entails? Since the bulk of it occurs among already impoverished people, it means hunger, and famine, malnutrition of children, and high infant mortality. Dr. Balfour has estimated the direct economic loss to the British Empire, due to illness and mortality from malaria, to be in the neighborhood of two hundred million dollars annually. In our own Southern States an estimate of a million cases of malaria a year is conservative. Some years ago Dr. L. O. Howard, for many years the Chief of the U. S. Bureau of Entomology, estimated the annual financial loss in the United States from malaria to be not less than one hundred million dollars.

If malaria means that much to the human race, it must be admitted that a discovery which makes possible the control of it must also be considered of vast importance, and that is what Ross's discovery did. Of course Ross's "discovery" was by no means comparable with striking oil when digging a cesspool, or stumbling over a treasure chest when strolling in the moonlight with a sweetheart. In the introduction to his *Memoirs* Ross quotes a friend of his who epitomized the popular notion of scientific research by picturing a scientist consulting his watch and exclaiming "Ha, half an hour to spare before dinner; I will step down to my laboratory and make a discovery." Ross reminds us that our books of science are records of results rather than of the sacred passion for discovery which leads to them. "Yet," he says, "many discoveries have really been the climax of an intense drama, full of hopes and despairs, visions seen in darkness, many failures, and a final triumph: in which the protagonists are man and nature, and the issue a decision for all the ages." Ross is thus describing his own discovery, which came after years of toil, after hundreds of discouraging failures, and after repeated heart-breaking interruptions and exasperating interferences. But even those years of persistent labor, crowned at last by successful observations and experiments, were only, as it were, the turning of a key in the lock. Prior to this it was necessary to find the way to the door where the lock was situated, and to be in possession of a key that would fit the lock. Hundreds of observations, speculations, and collateral discoveries were necessary to point the way and clear the road. Before telling you of Ross's work I would like to give you a brief outline of the earlier history of malaria.

This disease, which is now recognized as the most important one with which the human race has to contend, not even excepting tuberculosis or hookworm, was well known to medical writers among the ancients. They, and practically everyone else up to the close of the nineteenth century, were well aware of the association of malaria with low marshy places. As its name implies, it was believed to be due to some poisonous quality of the air arising from such places, to which the name miasma was given. Many of the attributes, habitats and vagaries of this deadly miasma had been worked out with surprising accuracy.

We must not suppose for a moment that the possible instrumentality of mosquitoes in the spread of malaria had never occurred to any of the millions of people who through the centuries have suffered from and struggled with malaria. It is by no means a rare occurrence for popular beliefs which are long ridiculed or ignored by science, eventually to be proved correct. Thus it has been with the mosquito theory of malaria transmission.

It was in 1880 that the scientific study of malaria really began, for it was in that year that Laveran, a French army surgeon in Algeria, observed the minute parasites in the red blood corpuscles of malaria patients, which he recognized as the cause of the disease. There followed a differentiation of the several different species, and a study of the cycle of development which takes place in the human body, each recurring paroxysm of chills and fever being found to be coincident with the liberation of a new brood of young parasites from the blood corpuscles in which they had been developing for forty-eight or seventy-two hours, according to the variety of malaria. Laveran himself expressed belief in the mosquito transmission of the disease in 1884; the great German bacteriologist, Koch, did likewise in 1892; and in 1894 Dr. Patrick Manson, who had distinguished himself in the study of tropical diseases in China, also expressed belief in the mosquito theory.

Besides these researches, speculations and observations with respect to malaria itself, there were certain other discoveries which must be recognized as having contributed, if only as precedents or suggestions, to the elucidation of the malaria problem. One of these was the discovery by Patrick Manson, in 1878 and 1879, that mosquitoes were involved in the transmission of filariæ, which are small worm parasites living in the lymph glands and ducts of human beings. Had Manson completed his observations on the life cycle of filariæ he might have made a better guess than he did with respect to the mechanism of malaria transmission, and have saved Ross many an hour of hard work.

Another piece of work which influenced research on malaria was that of Theobald Smith and Kilborne on the transmission of Texas Fever of cattle by ticks. These American scientists did what Manson might have done, but didn't; they showed, in 1893, exactly how an insect served in the transmission of a blood disease from one animal to another. But in this case the transmission takes place through the offspring of the infected ticks, the germ of the disease being passed on to them, through the eggs, from their infected mothers. Although this work of Smith and Kilborne served as a very suggestive precedent for the mosquito transmission of malaria, it also was the cause of many a wasted bead of sweat from honest labor in its suggestion of a possible hereditary transmission in the case of the mosquitoes.

Now, although Manson gets a great deal of credit for formulating the theory that mosquitoes carry malaria, as we have seen he was by no means the first to lay his bet on the right number, and as a matter of fact Manson's guess wasn't as near right as some of the earlier guesses, for he thought that the malaria parasites, after being sucked into the body of the mosquito, turned into resistant spores which, when the mosquito died and fell into water, survived in this water until they eventually found their way into another human being's stomach. The important thing that distinguished Manson's theorizing from that of others was the fact that he theorized in the ear of an adoring disciple who was violently enthusiastic by nature, was endowed with more than usual perseverance, and, being an officer in the Indian Medical Service, was in a position to do some experimental work on the subject. That man was Major Ronald Ross. There is no very good reason why Patrick Manson could not himself have tested his mosquito theory in London, where he was in contact with plenty of malaria cases returning from the seven seas, but he had a pleasant and growing practice in London, and apparently preferred to inspire someone else to do the work for him.

Now let us go back and see what manner of man this was who was undertaking to prove Manson's theory. Born in a hill station in India on Friday, May 13th, 1857, the son of a British army officer, Ronald Ross spent the first eight years of his life in India and was shipped back to England for the sake of his health and education. However, Ross himself remarks in his *Memoirs* that the money his parents spent on his education was largely wasted. His father chose medicine as a profession for him, and he finally resigned himself to his father's wishes, although he claims to have had no predilection for medicine and more or less looked down upon it. He burned the midnight oil composing music and writing poetry and epic dramas instead of studying anatomy, and consequently, although he succeeded in passing an examination for membership in the Royal College of Surgeons after only three days of feverish study, he failed to pass the easiest medical qualification he could try for, having begun studying for it on the morning of the examination. After that he spent a year as a surgeon on a transatlantic vessel but spent his time mostly in studying life and writing dramas and poetry about it. To make a long story short, he finally passed his examinations for the Indian Medical Service, near the bottom of the list, and spent the next thirteen years of his life in various Indian cantonments, hospitals, and military posts as a medical officer, fumbling feebly at his professional work, but laboring fervently and feverishly, even to the point of injuring his health, first at poetry and drama, then at complicated mathematical propositions and theories, with the aid of which he attempted to work out a theory of the universe, and then back to literature again.

Although Ross never became preëminent either in literature or mathematics, his achievements in both fields are far from mediocre.

It was not until 1890 that Ross finally determined actually to labor at his profession; after reading some medical books and journals he found he could not obtain much help from them so, as he had done in other lines, he energetically set out to do things for himself. He decided that malaria was a sort of intestinal disturbance and wrote four papers on the subject. He decided that Laveran was all wrong about the malarial parasites, and also that the miasma theory was wrong, and wrote four more papers exposing these errors. But he soon drifted back into literature and mathematics and decided that when he got his pension in 1897 he would adopt literature as a profession.

In 1894 Ross got a year's furlough to England, in the course of which he met Dr. Manson and had his exuberant enthusiasm and energy directed towards malaria and mosquitoes instead of meters and mathematics. After his arrival at his station in Secunderabad in Southern India he went at his task with wild excitement and almost frenzied enthusiasm. He knew nothing about the kinds of mosquitoes, or how to take care of them, or how to handle them, or what to look for in them. As a consequence he worked blindly and made many unnecessary errors, but he stayed with the job. He differentiated various kinds of mosquitoes according to a system of his own, he learned how to breed and care for them, he found out how to make them bite even though, as he expressed it, they were as stubborn as mules, and he became expert in dissection and microscopic examination. In examining mosquitoes for possible developmental stages of malaria parasites he says he searched every micron with the same passion and care as one would search some vast ruined palace for a little hidden treasure. After having examined many hundreds in this way without result, and with no assurance that there was anything to find, a lesser man's passion and care would have gotten frayed at the edges before the search was finally rewarded. He kept Dr. Manson informed of all his doings, and in return got advice and directions and encouragement from his hero. Manson told him to consider himself a Sir Galahad looking for the Holy Grail.

Three long hot months he spent in feeding mosquitoes on malarial blood and endeavoring to find out what happened to them in the mosquito, but alas! he was using kinds of mosquitoes which are not involved in human malaria and made little progress. Following Manson's suggestion he let mosquitoes which had fed on malarial blood die in a little bottle of water, and then gave some natives backsheesh to drink the water. Eleven days later one of the natives got sick and had fever for three days, but there were no malaria parasites in his blood, so he rightly concluded that this was a false alarm. Finally, after failing to follow the so-called flagellated spores into the tissues of the mosquito, or anywhere else, he decided to keep his insects alive for a few days after feeding on his patients and then see what there might be to see. This time he was sidetracked by another protozoan parasite of mosquitoes. He spent long weeks studying this in the hope of connecting it with malaria, but without success. Then came an interruption while he was delegated to control an outbreak of cholera in Bangalore. In 1896 he began to form some notions of his own, and wrote Manson that the belief was growing on him that the mosquitoes transmitted malaria by their bites. He did some experiments to find out, but as he only kept his mosquitoes a few days after feeding, the results were negative. Finally in 1897 he got hold of some brown dapple-winged mosquitoes, and on the 20th of August of that year, when about to give up his labors for the day early on a hot muggy afternoon, he decided to examine one more mosquito. This time, to use his own words, the Angel of Fate fortunately laid his hand on his head, and he discovered in this mosquito some cells which he recognized at once as developmental stages of the malaria parasite. That evening he wrote some more verses to his poem "In Exile," which, as amended a few days later, read as follows:

This day relenting God
    Hath placed within my hand
A wondrous thing; and God
    Be praised. At His command,

Seeking His secret deeds
    With tears and toiling breath,
I find thy cunning seeds,
    O million-murdering Death.

I know this little thing
    A myriad men will save.
O Death, where is thy sting?
    Thy victory, O Grave?

During the later years of his life Ross always celebrated the 20th of August as the anniversary of "Mosquito Day."

After another interruption Ross resumed his work on malaria in Calcutta in February, 1898. Failing to make any progress on human malaria, he began working on bird malaria; by the latter part of April he had proved beyond question that the malaria parasites undergo development in the mosquitoes, and by the early part of July he made an even more important discovery:—by tracing the development in the bodies of infected mosquitoes he discovered the production of thousands of spore-like bodies which invaded the salivary glands of the mosquito and were injected with its bite, from which he deduced, rather hesitantly and almost apologetically, since it was contrary to Manson's ideas, that malaria was transmitted to birds by the bites of mosquitoes, and at once he proved it by actually infecting healthy birds by the bites of his infected mosquitoes. Few seemed to doubt but that what Ross had proved for bird malaria would also be applicable to human malaria, although Manson himself remarked, "One can object that the facts determined for birds do not hold, necessarily, for men." Subsequent work proved that Ross's work on bird malaria does hold for human malaria as well, only in different kinds of mosquitoes. But unfortunately Ross was not the one to put this crowning touch to the work. Dame Fortune, as Ross writes in his *Memoirs,* did nothing but buffet him about for the remainder of his time in India. First she sent him the so-called "black spores" to worry him for weeks, then she gave him one of the few species of Anopheles which does not carry malaria. She continued a plague scare which aroused popular prejudice against any experimental work on human beings. She made the Royal Society refuse to send him help. She instigated Surgeon General Harvey to interrupt his work for months on the kala-azar inquiry in Assam; and lastly, to quote Ross, "She arranged that some ingenious Italian gentlemen should pirate most of my results in the interval."

Demonstration of the fact that malaria is transmitted only by the bite of certain kinds of mosquitoes, of course suggested at once the possibility of control if not actual eradication of the disease by attack on Anopheles mosquitoes. On his way home from India in 1899 Ross meditated over the practical application of his work. "In two years," he said to himself, "we shall stamp malaria out of every city and large town in the tropics, at least if they possess sanitary departments as in British possessions." Wherever there was a white man or trained inspector to command, and a few coolies to work, it could be done. This, Ross asserts, was not the dream of a visionary, but a carefully reasoned statement of a man who knew from experience with other sanitary projects what he was talking about.

It was not long before it was abundantly demonstrated that Ross was right in believing that the control of malaria could be accomplished, but it has also been demonstrated that he was wrong in believing that it would be. It is a project which costs money, requires interest on the part of governments, and a popular demand. Where these requirements have been found, malaria has either been abolished or reduced to a small fraction of what it once was.

The first anti-malaria campaign was begun in Havana in 1901. There were no precedents, no handed-down information, no previous successes or failures to lead the way, but Colonel, later General, Gorgas, who conducted the campaign, was a genius in sanitation, and he made a triumphant clean-up of malaria in that Cuban city. From 1890 to 1900, in a population of 350,000, there were 5,643 deaths from malaria; from 1900 to 1910 there were 444 deaths in a much larger population.

Meanwhile Ross himself was doing his utmost to get the British or Colonial Governments to act, but without success. Finally, in 1901, Ross organized an expedition of his own to West Africa, financed by private funds of a backer, to demonstrate to a skeptical world the possibility of actually controlling mosquitoes at a reasonable cost. This expedition was successful, and was followed soon after by an equally successful demonstration at Ismailia on the Suez Canal.

But the most striking example of what can be done in the control of mosquito-borne disease is the transformation of the Canal Zone in Panama from a White Man's Graveyard to one of the healthiest localities in the world. The work in Panama has been described by a great British sanitarian who did a similar job in Malaya, as the greatest sanitary achievement the world has ever seen. The French attempt to build a canal across Panama was wrecked by malaria and yellow fever, both mosquito-borne diseases; the graves of fifty thousand laborers were dug, but no Panama canal. Shipload after shipload of laborers, engineers, nurses, and doctors were sent to this pest hole, the lives of the majority to be snuffed out in a few weeks or months. One vessel is reported to have brought over eighteen young French engineers, all but one of whom died of yellow fever within a month. In 1904 the Americans bought the French rights and set to work, with Colonel W. C. Gorgas as Chief Sanitary Officer. As a result of his application of the recently acquired knowledge concerning yellow fever and malaria, the last case of yellow fever ever to develop in Panama occurred in September, 1905. In 1906 the average rate of hospital admissions for malaria each month was 6.83% of the canal employees. Year by year it dropped until in 1913 it was 0.64% per month, less than one-tenth what it had been seven years earlier. Colonel Gorgas himself wrote to Ronald Ross the following words: "It seems to me not extreme therefore, to say that it was your discovery of this fact (the transmission of malaria by the bites of mosquitoes) that enabled us to build the Canal on the Isthmus of Panama." It is that same discovery which will some day bring about the conquest of the tropics, the prevention of millions of human deaths per year, and the elimination of an unimaginable amount of human suffering.

ASA C. CHANDLER.

VI

RACIAL CHANGES AND THE GENE

IT WAS not known precisely how an animal or plant reproduces until the microscope was invented. It was then seen that all living substance consists of microscopic units known as cells, each containing a spherical body known as the "nucleus" (see Fig. 1). It was also seen that reproduction takes place through cells. A "sperm" cell from the male combines with an egg cell from the female, at the time of mating (see Fig. 2). The product of the union is the "fertilized egg." From this the offspring develops. Further studies with the microscope showed how development takes place. The fertilized egg divides into two cells, and each of these again divides into two, making four cells. Next eight cells are formed, then sixteen, thirty-two, sixty-four, etc.; and the process of cell division is continued until the trillions

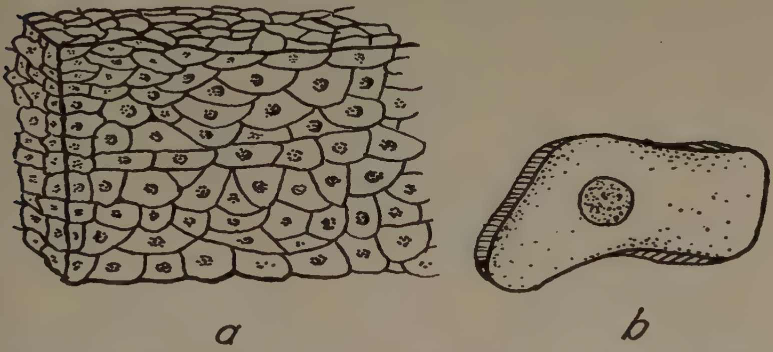

FIGURE 1. Cells (from the lining of the throat); *a,* mass of cells, magnified about 300 times; *b,* a single cell, more highly magnified.

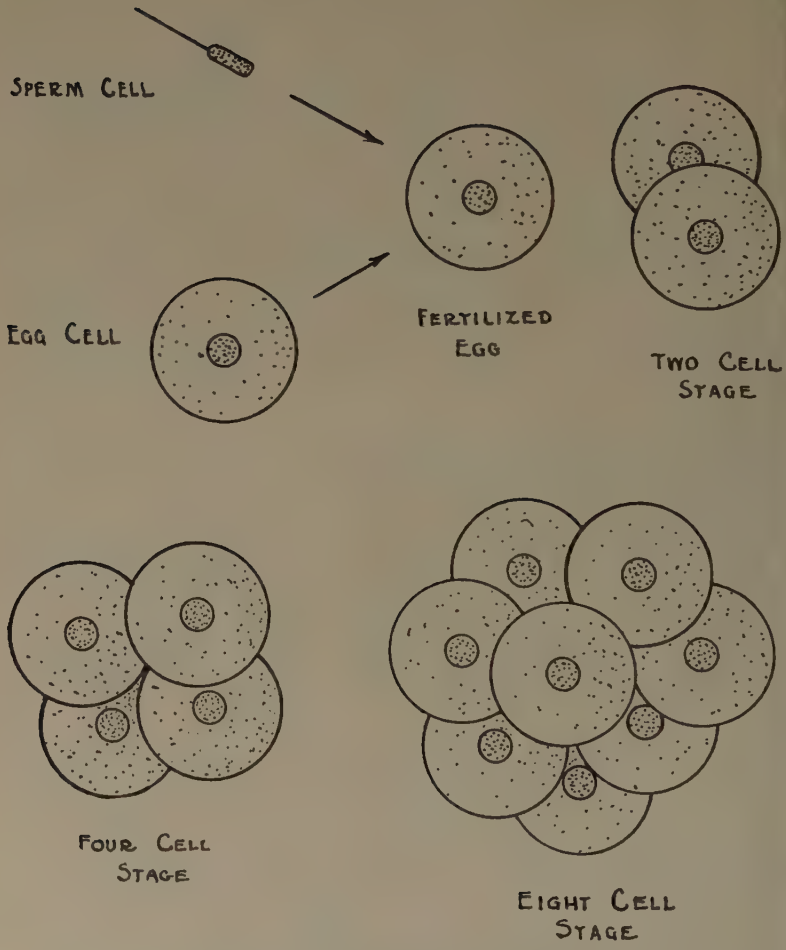

FIGURE 2. Fertilization and development.

of cells are formed that constitute the adult body. Thus reproduction and development take place.

But how and what do the offspring inherit from their parents? Here again the microscope was of assistance. As it became more perfect, it could penetrate further into the cell, and it showed that cells in general contain in their nucleus certain structures, usually rod-shaped, that are known as chromosomes (see Fig. 3). The reproductive cells, like other cells, contain chromosomes, and when sperm and egg combine at the time of fertilization, their chromosomes persist in the fertilized egg (see Fig. 4). In some way, not at

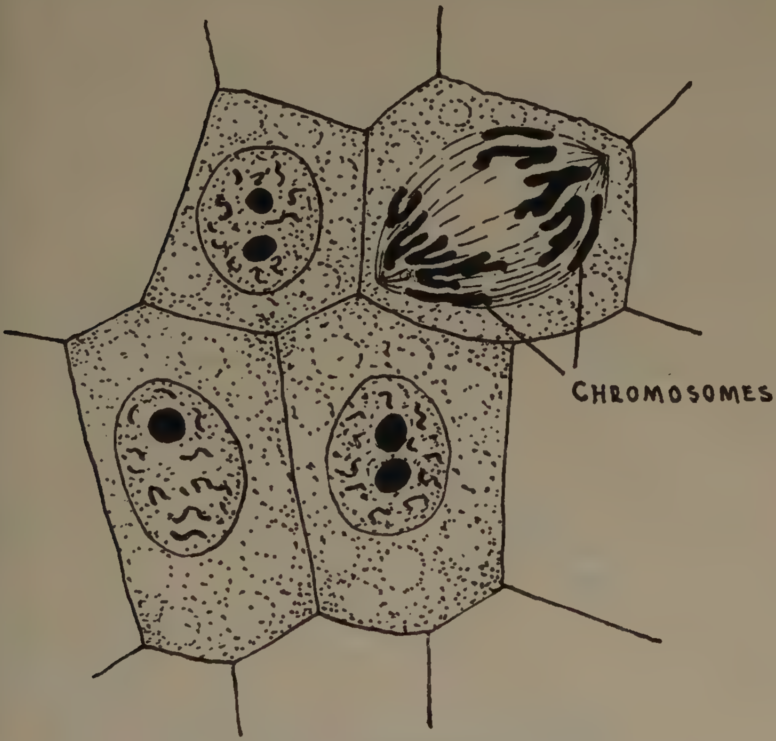

FIGURE 3. Cells, one showing chromosomes.

present understood, the chromosomes cause the fertilized egg to develop into a new individual that resembles its parents. Chromosomes therefore constitute the material basis of inheritance, in the sense that they are the bodies that pass down from one generation to the next, and that cause the offspring to resemble their parents (under similar conditions).

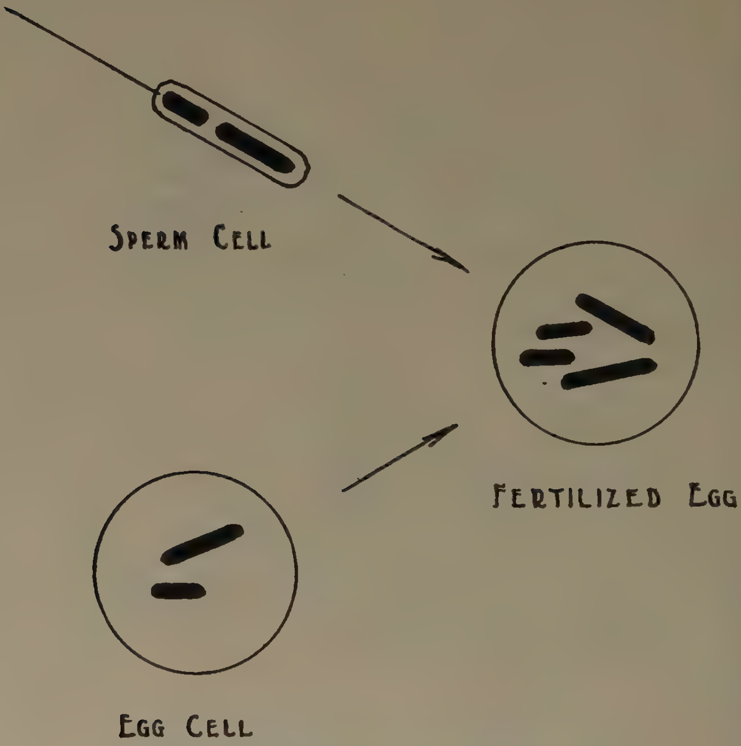

FIGURE 4. The inheritance of the chromosomes.

Breeding work has shown that the chromosomes contain certain bodies, not visible under the microscope, that are known as genes (see Fig. 5). These are the ultimate units of heredity. They are arranged in linear order, like beads on a string. Genes in different parts of a chromosome differ in their effects on development, and so presumably are not exactly alike in constitution. All genes, however, have the power of growth and division. The chromosome itself multiplies (at certain times) as a result of the growth and division of its individual genes.

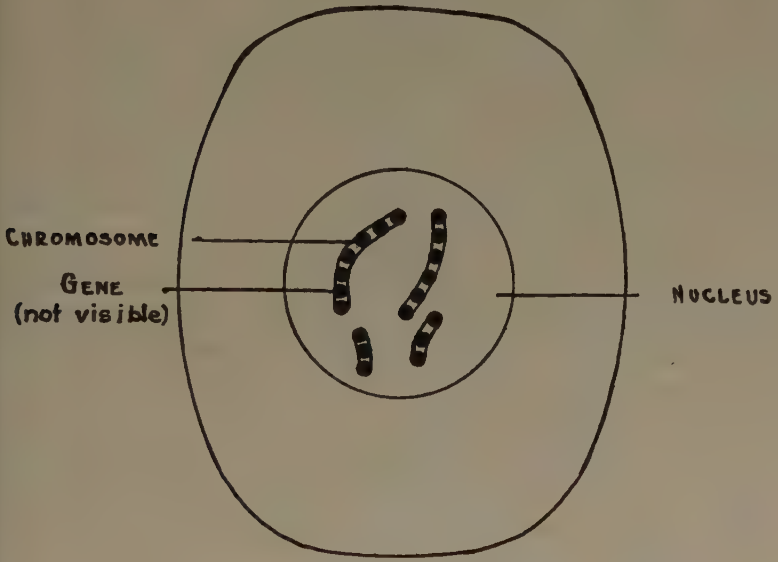

FIGURE 5. Schematic representation of chromosomes and genes.

The reproductive cells of every species contain a definite number of chromosomes. In the case of man, a sperm cell contains twenty-four chromosomes; an egg cell, the same number. No two chromosomes within a given reproductive cell are alike in regard to their genes. The chromosomes of the sperm and egg cells, however, correspond with each other, as is often evident from a comparison of their sizes. For example, if the sperm cell contained three chromosomes of different sizes, say large, medium, and small, the egg would also be found to contain three chromosomes of the same sizes.

The fertilized egg has twice as many chromosomes as the reproductive cells, since it arises by the union of two reproductive cells. For example, in man each reproductive cell has twenty-four chromosomes, and the fertilized egg has twenty-four plus twenty-four, or forty-eight chromosomes. These run in pairs. For, the reproductive cells had one chromosome of each kind; and therefore the fertilized egg has two. Thus, if the sperm and egg cell each had a short, medium, and long chromosome, the fertilized egg would have a pair of chromosomes of each size.

Consider now what the chromosomes do when the fertilized egg starts to develop by cell division. Before the fertilized egg divides, its chromosomes line up in the middle of the cell and each of them splits lengthwise into two (see Fig. 6). Next the split halves separate to opposite sides or "poles" of the cell. The division of the cell proper now takes place, in between the separated chromosome halves. Thus two new cells arise. The process of cell division, as just described, is known as "mitosis."

It will be seen that when the fertilized egg divides, each "daughter" cell receives a half of every chromosome present in the parent cell. The halves of any one chromosome, formed by splitting, are identical in kind with each other, because the genes are arranged in linear order within the chromosome, and further because the splitting of the chromosome involves the division of each of its genes, in the plane of the split.

The new cells formed by mitosis resemble the parent cell in every detail, as regards their chromosomes and genes. Each has the same number and kind of chromosomes as the fertilized egg. For, the one set of forty-eight in the fertilized

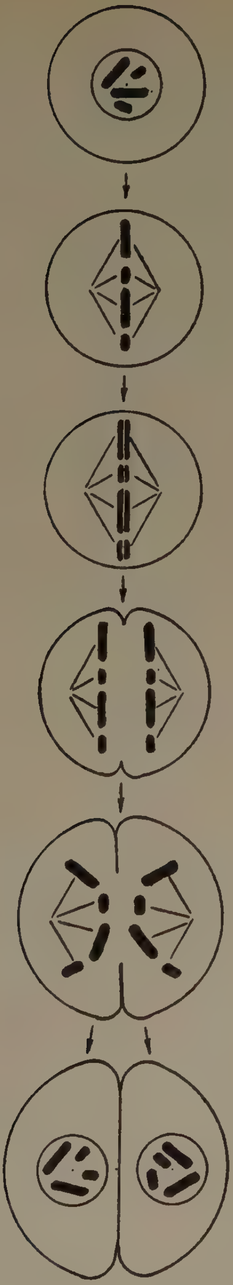

FIGURE 6. Cell division.

egg became two sets of forty-eight through the splitting of its chromosomes, and one set went to each of the daughter cells. Thus the fertilized egg divides to form the first two cells. These in turn divide in the same way as the fertilized egg. As a rule, whenever a cell divides, all of its chromosomes first split into two and it then forms two new cells identical with itself in chromosomal make-up. Therefore, all the hereditary material comes to be distributed among all cells of the adult body that arise through mitosis.

The reproductive cells, like other cells, arise through division. But there is an important difference in the way they receive their chromosomes in cell division, as compared with other cells. The formation of the ripe reproductive cells is preceded by a special type of cell division, known as the "reduction division," whereby the chromosome number is halved. In the case of man the number is reduced from forty-eight to twenty-four.

The reduction division takes place in a very definite way (see Fig. 7). First the chromosomes move to the middle of the cell, but instead of splitting lengthwise into two, they come together in pairs, forming twenty-four pairs (still using the numbers that apply to man). Next, the members of each pair separate to opposite poles of the cell so that there are now twenty-four chromosomes at each pole. Cell division then takes place in between the two sets of twenty-four. Thus two cells are formed, each with twenty-four chromosomes instead of forty-eight. If the number were not reduced, but remained forty-eight in the sperm and egg cells of a given generation, a fertilized egg of the next generation would have forty-eight plus forty-eight or ninety-six chromosomes, and so would have double the number characteristic of the previous generation. But the reduction division prevents a doubling in chromosome number from one genera-

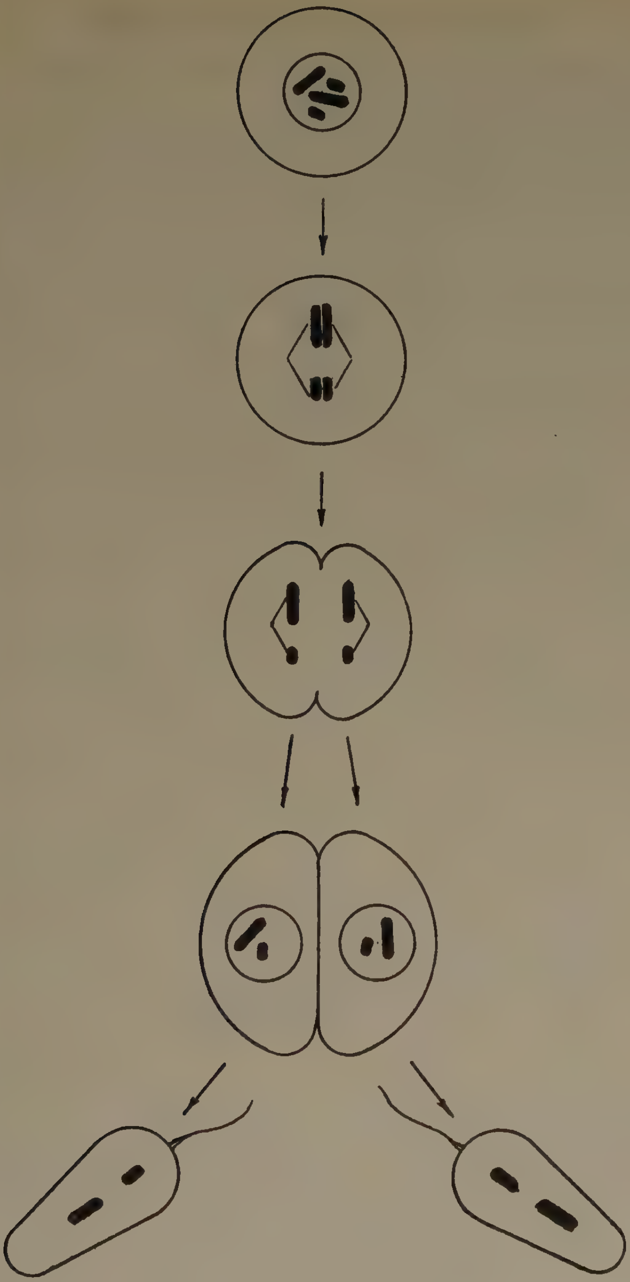

FIGURE 7. The reduction division.

tion to the next. The reproductive cells always have twenty-four chromosomes, the fertilized egg forty-eight (in man). Moreover, the reduction division results in separating the members of each pair of chromosomes from each other, so that a given reproductive cell has only one member of a pair, not both.

The fertilized egg requires for its development certain outside conditions, such as food, air, a certain temperature, etc. These we may refer to as the environment. During the course of development, traits appear, such as eyes, eye color, stature, etc. The traits of an individual are the product of both heredity and environment. This we know from the fact that the fertilized egg cannot develop either in the absence of its chromosomes or in the absence of certain external conditions.

Some people do not believe in heredity. They claim everything is a matter of environment. Such a viewpoint is hardly tenable. A man's dog does not resemble him to the extent that his child does, even though dog and child may have been living in very much the same environment. Obviously, there is such a thing as heredity. It varies with different species, and even within a given species, though to a lesser extent. Child and dog do not have the same kind of chromosomes. That is why they develop differently, even though they grow up in substantially the same environment. On the other hand we know that a child's development is influenced by food, air, education, etc. Therefore, environment also plays a part in development. It is, in fact, absurd to set environment against heredity, and ask which is the more important. The individual begins his life as a miniature bag of chromosomes—the fertilized egg. Change either his chromosomes or his environment, and you change his development.

It is not strictly correct to say that a child inherits his blue eyes; for blue eyes are not in the fertilized egg. What the child really inherits are the genes for blue eyes. These cause blue eyes to develop under a certain set of external conditions. By heredity we mean the transmission from parent to offspring of certain material bodies that cause the offspring to resemble their parents under similar conditions of development. Traits are not inherited. They develop.

Any trait is dependent in development upon numerous genes. For example, in the insect Drosophila, eye color is dependent upon at least twenty genes. So are wings, bristles, etc. The genes for a given trait are not all bunched together in a given chromosome. On the contrary, they are scattered quite at random throughout all the chromosomes. Neither are the genes for two different traits arranged in any definite manner with regard to each other. An eye gene might be next to a wing gene in one chromosome, but next to a bristle gene in some other chromosome. A given gene does, however, occupy a definite position in a chromosome. This is known as its locus. In Drosophila, the loci of many genes have actually been determined. This has been done through breeding experiments.

Genes usually remain unchanged from one cell division to the next, and from one generation to the next. But occasionally a gene changes; that is to say, it *mutates*. As a result, a new type of animal or plant might arise; as, for example, a wingless race of flies, or a brunette of pure white parents.

We cannot actually see a change in a gene itself, because genes are too small to be visible. All that we can see is the effects of the change on the development of an animal or plant, such as the change in the wings or in color, just mentioned. We speak of the change in the gene itself as a *mutation;* and of the new type that results from that change, as a *mutant.*

Striking changes, due to mutation, have been known to practical breeders for a long time and have been referred to as "sports." An example of breeders' sports is the short-legged race of sheep known as the Ancon breed.

More recently, the small insect, Drosophila, has been intensively studied for mutations. The genes affected by mutation have been located in the chromosomes, through breeding work. Drosophila has four pairs of chromosomes. These have been arbitrarily numbered and referred to as the first, second, third, and fourth chromosomes. Several dozen mutations have taken place in each of the larger chromosomes during the period that Drosophila has been under observation in the laboratory. For example, a mutation in the first chromosome caused the eyes to change from red to white. The mutation took place in a gene located in the "left-hand" end of the chromosome, at locus 1. Another mutation, at locus 33, caused the wings to change from long to "miniature." A third mutation, at 56, caused the bristles to change from straight to "forked."

A mutation as a rule takes place in just one cell of a given individual and in just one gene of that cell. It may spread to other cells through cell division. The extent to which it spreads depends on the extent of the cell division. In general, the earlier a mutation occurs in development, the greater the number of cells to which it spreads.

A mutated race can be crossed to the normal race, and so hybrid offspring can be produced. For example, a wingless race of flies might be crossed to the normal winged race. The offspring are hybrids. They contain both the mutated gene of the wingless race, and the unmutated gene of the normal race. When the hybrids breed with each other, they reproduce both the normal and the mutant races, usually in the ratio of 3 normal: 1 mutant. From the fact that the hybrids are capable of producing mutant offspring, we conclude that the mutated gene did not mix with the unmutated gene, in the hybrid.

It is possible to combine different mutant types by crossing. For example, you can cross a white-eyed race of flies with one that has short wings and in a later generation get a race that has both white eyes and short wings (instead of the normal red eyes and long wings). To the white short race still other mutant traits can be added by crossing, so that eventually a new type may be got that contains many mutations and looks extremely different from the normal race.

Not all departures from the normal are due to mutations, even in a pure stock. Everybody knows, for example, that an exceptionally well fed animal may be larger than normal, even though it comes from a pure stock. The increased size of the well fed animal is an *acquired trait*. It is not due to mutation, and is not inheritable. Before any variation can be definitely regarded as a mutation, it must be shown that it is inheritable. Most variations from the normal, in a pure bred stock, are acquired traits. Mutations, on the other hand, are rare in origin. They may, however, become abundant through reproduction.

In Darwin's day the changes that were constantly being produced by the environment were not clearly recognized as acquired traits. They were referred to as "fluctuating variations." Darwin thought that they were due to a constant variation of the germ plasm, and that they were inheritable. Darwin knew of mutations, but he thought that they were exclusively large. He thought too that as a rule they could not lead to evolution, both because they were large, and because they were rare. The fact that they were large, he argued, would as a rule make them injurious; and the fact that they were infrequent would lead to their gradual elimination, since they would have to cross with the more abundant normals and in so doing they would gradually approach the normals, through mixture of the germ plasms.

Darwin was correct in arguing that large changes, at a single stroke, would as a rule be injurious, for they would in all likelihood necessitate numerous readjustments in many parts of the organism, and they would not allow time for such readjustments. But we now know that mutations are not always large. We know too that they do not become "diluted" through a mixture of germ plasms. Finally, we know that we must distinguish between non-hereditary changes or acquired traits, and actual hereditary changes or mutations. The first kind of change (non-hereditary) cannot lead to racial change. The second kind (mutation) can.

A comparative study of the mutants of Drosophila brings out a very important point. It shows that there is no regularity of any sort connected with their production. Take the eye color mutations. Among various other changes produced by mutation one might observe some that lead to the lighter eye colors, and it is possible to arrange them in a series from red through the lighter and lighter shades to white. But they do not arise in this order. Thus, if we arrange the mutants in order from red to extreme white and number them 1, 2, 3, 4, 5, then 5 might turn up first, 2 next, etc. Moreover, if 3 turned up first, and itself mutated again, it would not necessarily mutate to a still lighter eye color, 4, but it might go back towards the normal. In other words, the occurrence of one mutation does not determine that the next shall be in the same direction.

Moreover, mutations cause all sorts of changes in an organ, not just one kind. For example, in Drosophila the eyes sometimes become darker rather than lighter, or even change towards a different kind of color, such as purple. The wings might be shortened, bent, changed in venation, etc. Mutations therefore are of all sorts and in absolutely no relationship to each other; they are *random* changes. They are more often harmful than beneficial, but that is what one would expect of random changes in a complex organization.

How could the advance towards a higher type ever result from blind changes of this sort? We find our answer in the simple fact that in nature the bad mutants die, leaving only the occasional good mutants; that is, the ones that represent a better adjustment to a given environment. The dying out of some types and the survival of others we may call natural selection.

Until very recently the causes of mutation were entirely unknown. All attempts to produce them artificially had failed, though many agents had been used, such as drugs, mechanical agitation, light of different colors, temperature changes, etc. Most of the results were negative and in only a few cases were positive effects claimed. But neither positive nor negative results were conclusive. The experiments were performed in such a way that if any mutations had occurred they would have escaped detection, for the most part. Moreover, when mutations were found, the experimenter often failed to indicate how many of the observed mutations would have occurred without treatment. And usually the numbers were too small to warrant any conclusion. Thus the causes of mutation were, until recently, unknown.

But in 1926 Professor H. J. Muller definitely produced mutations. This he did by means of X-rays. He overcame all of the difficulties in the earlier experiments and showed conclusively that mutations can be produced artificially and on a large scale. By subjecting flies to X-rays he produced a great number of mutations—in fact as the result of a few hours' treatment he obtained practically all the mutants that had previously been observed to arise naturally in the laboratory over a period of ten years. In addition he obtained many mutants never before observed.

The frequency with which the mutants appear is proportional to the dosage of X-rays employed. In one set of experiments the natural frequency was increased over one hundred and fifty times. In another set it was increased still further by greater dosage of X-rays. But when the dosage gets beyond a certain point, the sterilizing effect of the X-rays interferes considerably with the experiments. The source of the radiation used in producing mutations is a matter of indifference, provided the radiation is of sufficiently short wave-length. Thus radium also can cause mutations, for it gives off a form of radiation, known as "gamma" radiation, that is similar to X-rays, though of somewhat shorter wave-length.

How do X-rays cause the genes to mutate? Probably in the same way that they alter inorganic matter—by knocking electrons out of atoms. They thereby chemically "activate" the atoms, and make them capable of chemical change. If one or more atoms of a gene are activated, the gene itself might mutate through chemical alteration.

It is possible for X-rays to activate genes indirectly. For the X-rays might hit a molecule of some cell substance close to a gene and expel an electron from the molecule. The expelled electron in turn might strike the gene and deprive it of one of its electrons. Measurements show that the indirect effect is much greater than the direct effect.

Radiations similar to X-rays exist in nature and Professor Muller pointed out that such natural radiations must produce mutations in organisms not subjected to any artificial treatment. Some natural radiation comes from the earth, and is due to radium and other radioactive substances contained in rocks, such as pitchblende. Some rays, known as cosmic rays, come from the outside world, and are even more penetrating than the earth rays. Finally, animal and plant tissues themselves contain an element (potassium) that is slightly radio-active. The problem now was to find out whether all the various sources of natural radiation were sufficient to account for all the natural mutations.

Calculations made by Professor Muller in collaboration with Dr. Mott-Smith, of the Rice Institute, showed that natural radiation, from all sources, did not exist in sufficient amount to produce more than a small fraction of natural mutations. For the amount of the radiation coming from natural sources is somewhat less than 1/100,000 that of the radiation produced by the X-ray machine used in Professor Muller's experiment. If radiation is the sole cause of mutation, then the natural mutation rate should be under 1/100,000 that of the X-ray rate. It was found, however, that the natural mutation rate was disproportionately high (about 1/100 that of X-ray rate) showing that there must be important causes for mutations in nature, in addition to radiation.

Yet natural mutations are similar in their manner of occurrence and in their general character to X-ray mutations, and so it is very likely that the causes of the two are fundamentally of the same general character. Natural mutations are undoubtedly caused in part by radiation. But they are probably caused also by other ultra-microscopic disturbances of a random character, consisting of collisions between particles of matter (electrons, atoms, molecules). The work of ferreting out the various remaining causes of natural mutations is now being prosecuted along the lines thus suggested.

Heat is the only other agent thus far known to produce mutations, in addition to radiations of the shorter wavelengths. An experiment by Professor Muller and the writer in 1919 suggested that the mutation rate is doubled by an increase in temperature of ten degrees Centigrade. It has since been definitely shown by several other workers that heat produces mutations.

Now that mutations can be artificially produced, it can no longer be logically held that mystical causes are back of racial change. We see that a physical agent can produce mutations. The agent itself is definite. But the changes that it produces are of many different kinds; they are random changes.

It is conceivable that certain agents in the environment produce definite mutations. But in the present state of our knowledge we cannot predict what kind of mutations a given agent or a given environment will produce. For example, conceivably moisture might produce some definite kinds of mutations, but what these would be like, we do not know. It is true that animals which live in a moist environment often have webbed hands, but it does not follow that the moisture specifically causes the webbed mutations. In fact, we know that webbed hands occasionally appear in man and in other animals living in a dry environment, and it therefore seems reasonable to conclude that wetness does not necessarily cause the mutations in question. But wetness might *select* them, after they had arisen. In other words, wetness does not necessarily produce the mutations that it selects. The same thing is true of other environmental agents. We do not know at present whether all environmental agents can produce mutations. But even if we assume that they do, then we can be reasonably sure that if a given agent produced mutations of one kind, let us call them "a," it would in all likelihood not select "a," but rather some other kind, "b." In brief, the environment is not the same in its *causal* influence on mutations, as it is in its *selective* influence.

Since races change at present through mutation, it is reasonable to assume that they also changed in the past through mutation, and that they became adapted to their environments through the survival of mutations that happened to be effective; that is, through natural selection. In brief, the evidence as it now stands indicates that mutation in conjunction with natural selection is the method of evolution.

EDGAR ALTENBURG.

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